

# California

# MEDICINE

**JULY, 1948**

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OFFICIAL JOURNAL OF THE CALIFORNIA MEDICAL ASSOCIATION

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VOL. 69

JULY, 1948

No. 1

## Experimental Portacaval Anastomosis

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PORTAL hypertension, with its severe sequelae, has stimulated the ingenuity of surgeons for many years. The experiments of Nikolai V. Eck in 1877 established the foundation for the many portacaval shunting procedures that have been attempted. Direct portacaval suture anastomosis was done in France and Germany during the period from 1910 to 1912, but with poor results. Renal shutdown was the most frequent cause of death, and this was thought to be due to blockage of the inferior vena cava for too long a period. In other shunting procedures attempts were made to utilize small branches of the mesenteric veins and smaller venous channels such as the ovarian and spermatic veins. These suture anastomoses were not successful because the small vessels used did not allow sufficient flow of blood, thrombosis occurred and supportive measures that are available at the present time were lacking.

Many other procedures have been done in the hope of eliminating the hazards that result from portal hypertension. Direct cauterization of the varices, omentopexy, and attempted ligation of the small branches of the coronary vein have not met with notable success. Resection of the upper end of the stomach and lower portion of the esophagus for esophageal varices has been done with more successful results.<sup>7</sup> Splenectomy in cases of Banti's syndrome has resulted in occasional cures, but only when the obstruction of the splenic vein has been distal to the entrance of the coronary vein. The success in splenectomy is so variable that Blakemore<sup>1</sup> has urged surgeons to spare the spleen in those cases where the obstruction is proximal to the coronary vein, so that, if necessary, the patient may have the benefit of a splenorenal anastomosis.

The trying and tedious aspects of a portacaval anastomosis, as described by Whipple,<sup>9</sup> have been the stimulus for our experiments. We felt that if some of the technical difficulties could be overcome the

operation would be considerably less hazardous. Adequate exposure appeared to be an important part of this procedure. One of us had used a transverse incision in a retroperitoneal approach to the abdominal aorta<sup>4</sup> which provided excellent exposure, and we felt a modification of a transverse approach would be desirable in a portacaval anastomosis.

Blakemore and Lord<sup>2</sup> have stated: "There is full agreement that the ideal technique in blood vessel anastomosis embraces intima-to-intima coaptation without the interposition of a foreign body in contact with the flowing blood. It is conceded that suture anastomosis, when done with meticulous care, may closely approximate the above ideal." It has recently been shown experimentally by Johns<sup>5</sup> that suture anastomosis results in fewer failures than the non-suture technique. Blakemore and Lord felt that suture anastomosis was impractical for portacaval shunts because of difficulties of exposure and because complete occlusion of the vena cava for the length of time required for suture technique might cause serious kidney damage. It has since been stressed by Welch<sup>8</sup> and Blalock<sup>3</sup> that complete occlusion of the inferior vena cava is not necessary. The experiments here reported present a lateral approach to the portal vein and inferior vena cava and the use of a special clamp which permits occlusion of only a portion of the latter vein during the suture anastomosis.

### LABORATORY EXPERIMENTS

The present experiments were concerned with anastomosis of the end of the portal vein to the side of the inferior vena cava. Operations were carried out on 15 mongrel dogs weighing between 5 and 22 kilograms. Intravenous nembutal supplemented by ether was used for anesthesia. All dogs were intubated for the use of positive pressure anesthesia during the time that the chest was open. In the first six operations a right transverse subcostal incision was used which extended from the edge of the rectus muscle to the lumbodorsal muscle group and passed

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immediately inferior to the 13th rib. The 13th rib was resected and the 12th was severed at the transverse process. This approach resulted in better exposure than the usual longitudinal incision, but the hilus of the liver was still beneath the costal margin.

A thoracoabdominal incision was found to be more satisfactory and was used in the remaining dogs of this series. A right transverse incision was made along the 10th interspace through the costal cartilages anteriorly and extending to the lumbodorsal muscle group posteriorly. The pleura and peritoneum were opened and the diaphragm was incised in the direction of its fibers, lateral and posterior to the attachment of the liver. The hepatorenal ligament was cut and the kidney was pushed down. This approach provided excellent exposure of the inferior vena cava as well as the portal vein. The anterolateral surface of the inferior vena cava was dissected free from the entrance of the renal vein to the point where it passed beneath the liver. Dissection of the portal vein from the superior mesenteric to its bifurcation at the hilus of the liver was then accomplished.

A clamp (Figure 1) fashioned from a kidney pedicle clamp was used to occlude a longitudinal section of the inferior vena cava. A rubber-shod clamp was placed on the mesenteric vein proximal to the entrance of the splenic vein and the blood flow through the latter was controlled by a bulldog clamp. The two terminal branches of the portal vein were then ligated and the portal vein was divided (Figure 2). A longitudinal incision was made in the anterolateral portion of the vena cava, within the jaws of the clamp, to match the diameter of the portal vein. Both vessels were flushed out with saline and five zero Deknatel on a curved atraumatic needle was used for the anastomosis (Figure 3).

The following suture technique was found to be satisfactory. An everting mattress suture was placed at the hepatic end, and a new suture was placed along the posterior layer as an over-and-over continuous stitch. A second everting mattress suture was then placed at the caudal end of the anastomosis, the continuous suture was snugged up, and each of its ends was tied to an end of the mattress sutures. A continuous suture was then used for the anterior layer of the anastomosis and was tied in the same manner (Figure 3).

The clamps were removed in the following order: First the clamp on the inferior vena cava was removed, next the bulldog clamp on the splenic vein, and then the rubber-shod clamp on the mesenteric vein. After removal of the clamps, occasional slight bleeding occurred along the suture line, but this ceased spontaneously. The time required for completion of the anastomoses ranged from 12 to 40 minutes. No complications were attributed to the time taken in doing the anastomoses. Anticoagulants were not used in any of these experiments.

Dogs were sacrificed at postoperative intervals of one day to four months. Postmortem studies on all the animals of this series revealed only one case in which thrombosis had occurred. In this animal there

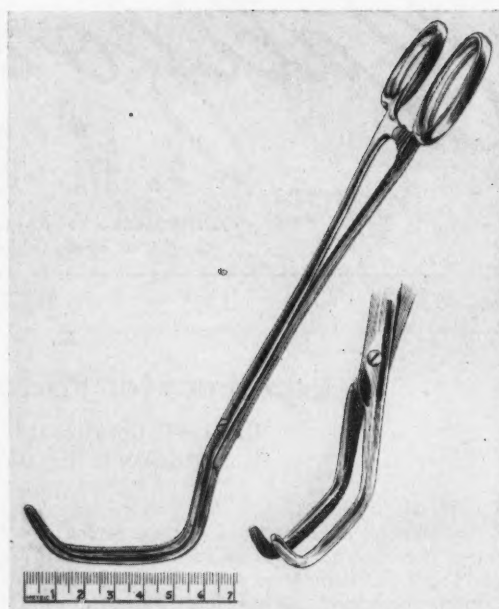


Figure 1.—Modified kidney pedicle clamp used to occlude a longitudinal section of the inferior vena cava.

was some angulation of the portal vein. The anastomoses in the remaining cases were patent with smooth intimal surfaces. The presence of suture material within the lumen along the line of anastomosis did not appear to be harmful. Satisfactory healing, demonstrated by microscopic sections, was present in all cases. No evidence of portal hypertension was found at autopsy, and in no animal could death be attributed to the operative procedure. Table 1 presents a summary of our experimental results.

In view of the difference in the human anatomy, it was felt that anatomical dissection should be carried out to determine the exposure to be obtained by the thoracoabdominal approach. Dissections were done on two cadavers and it was found that adequate exposure could be obtained by making the incision along the ninth interspace. The diaphragm was incised transversely and excellent exposure of the in-

TABLE 1

Dog No.	Date of Operation	Type of Procedure	Condition of Suture Line
1	December 16, 1946	Transverse Subcostal	Satisfactory
2	December 27, 1946	Transverse Subcostal	Satisfactory
3	May 26, 1947	Transverse Subcostal	Thrombosed
4	May 28, 1947	Transverse Subcostal	Satisfactory
5	June 9, 1947	Transverse Subcostal	Satisfactory
6	June 11, 1947	Transverse Subcostal	Satisfactory
7	June 11, 1947	Thoracoabdominal	Satisfactory
8	July 11, 1947	Thoracoabdominal	Satisfactory
9	July 21, 1947	Thoracoabdominal	Satisfactory
10	July 23, 1947	Thoracoabdominal	Satisfactory
11	July 24, 1947	Thoracoabdominal	Satisfactory
12	July 28, 1947	Thoracoabdominal	Satisfactory
13	July 29, 1947	Thoracoabdominal	Satisfactory
14	July 30, 1947	Thoracoabdominal	Satisfactory
15	October 2, 1947	Thoracoabdominal	Satisfactory

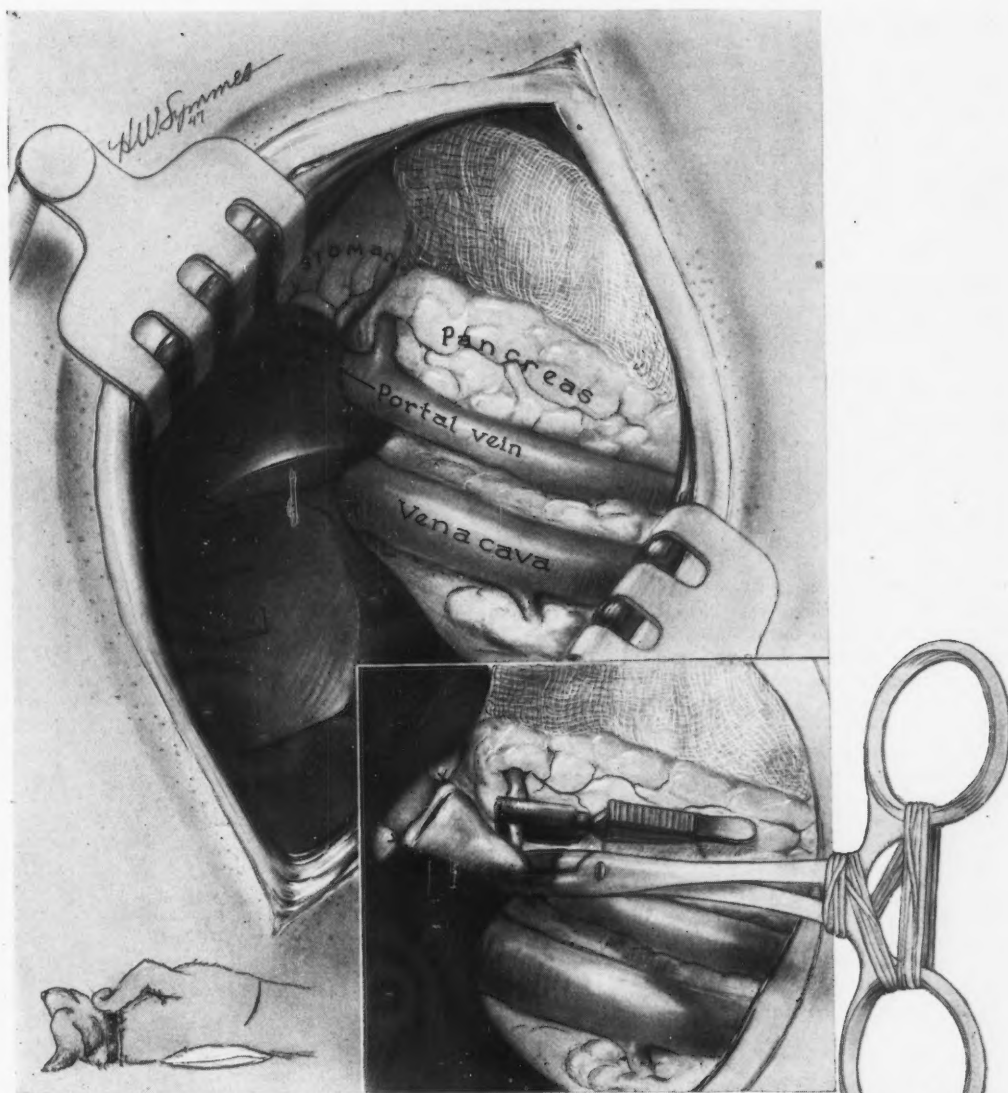


Figure 2.—Exposure in the dog of the hilus of the liver through a right transverse incision made along the tenth interspace; an inset shows portal vein ligated at its bifurcation and occluding clamps on mesenteric and splenic veins.

ferior vena cava as well as accessibility of the portal vein was obtained (Figure 4).

This procedure has been used on one patient with portal cirrhosis. A right thoracoabdominal incision was used and a direct portacaval suture anastomosis was done. This patient expired on the fifth post-operative day from hepatorenal failure. At autopsy the anastomosis was found to be patent (Figure 5).

An exploration was done in another patient through a right thoracoabdominal incision and the portal vein was found to be replaced by many small veins, a few of which were thrombosed. This was judged to be a cavernomatous transformation of the portal vein. It is now proposed to attempt a spleno-

renal vein anastomosis through an abdominal approach.

#### DISCUSSION

The clinical indications for this operation have been well discussed by Blakemore<sup>1</sup> and Whipple<sup>9,10</sup> and need be only briefly summarized. The patients are selected on the basis of liver function, the degree of disability, and the type of portal hypertension. Hypertension of the portal system is classified as to whether the obstruction is intrahepatic or extrahepatic, the former being due to cirrhosis, and the latter consisting of splenic thrombosis, cavernomatous transformation of the portal vein and various tumorous obstructions. In extrahepatic portal ob-

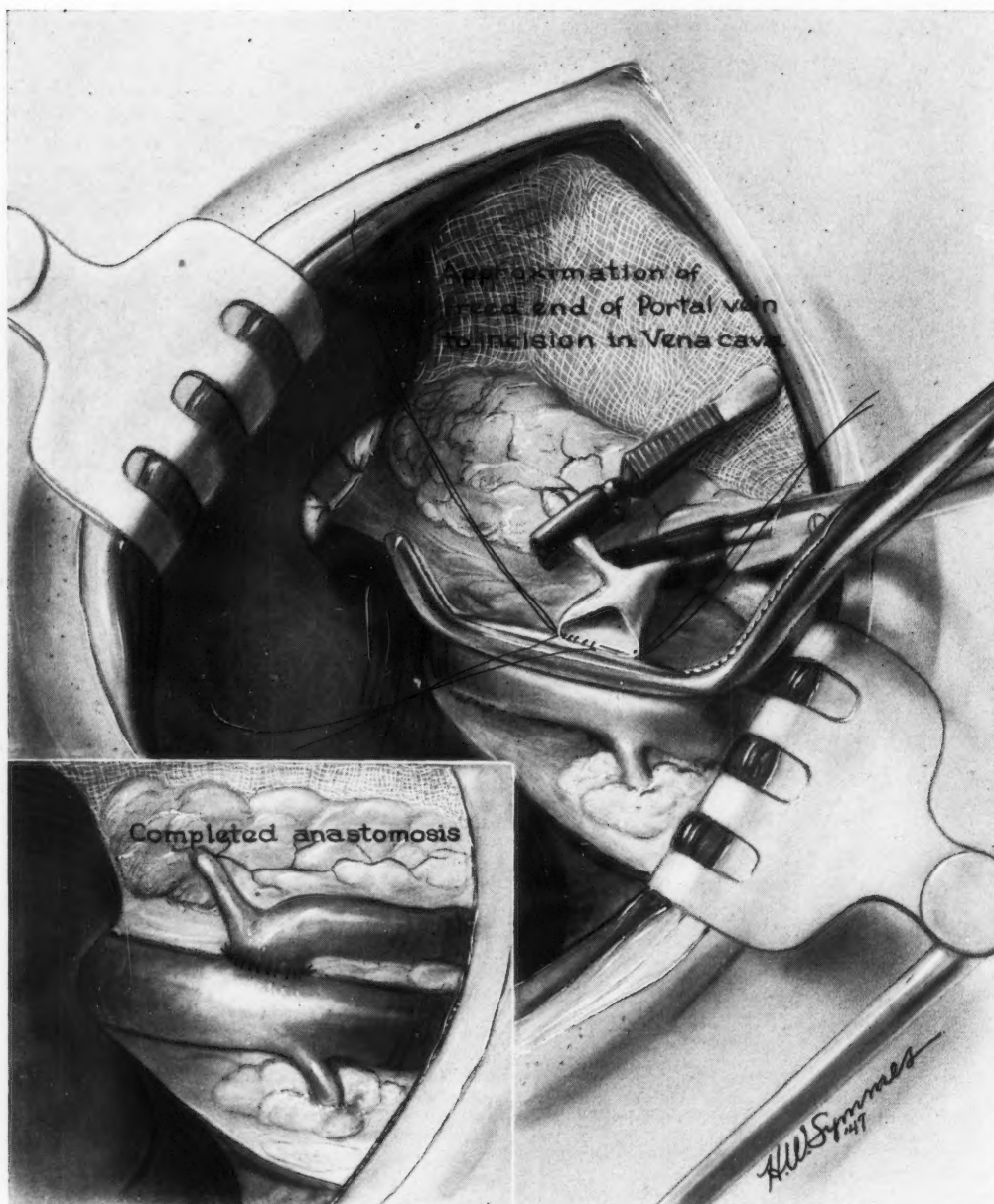


Figure 3.—Technique of end-to-side anastomosis of portal vein to inferior vena cava.

struction a splenorenal anastomosis is the procedure of choice, while in the intrahepatic obstructions a direct portacaval anastomosis would be in order.

There are cases in which the differential diagnosis of extrahepatic and intrahepatic portal obstruction is difficult, and occasionally a definite diagnosis can be made only at the time of operation. Because of this difficulty, Blakemore and Lord<sup>2</sup> and Blalock<sup>3</sup> have stressed the importance of taking manometric readings of the portal, mesenteric, and splenic veins

at the time of operation in order to establish the point of obstruction. The use of liver biopsies in clinically doubtful cases may be of considerable help. This technique is a relatively innocuous procedure and has been quite successful when adequately carried out (Volwiler and Jones<sup>11</sup>).

In those cases with extrahepatic obstruction in which the portal vein cannot be used for anastomosis, a right thoracoabdominal approach cannot be used. A left thoracoabdominal approach, especially in



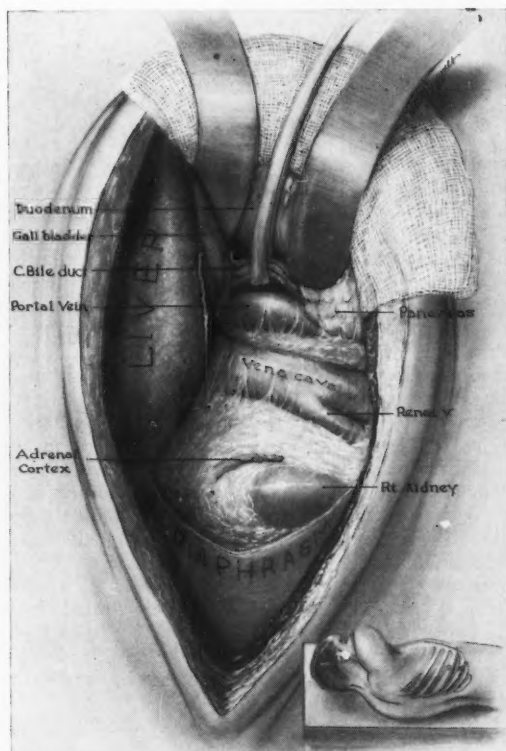


Figure 4.—Exposure of the portal vein and inferior vena cava obtained in the human through an incision along the ninth interspace.

cases where the spleen has previously been removed, has been suggested by Blakemore and Lord<sup>2</sup> for vein graft anastomosis of the coronary and renal veins. This approach was used by Linton, Jones and Volwiler<sup>6</sup> for combined splenectomy and splenorenal vein anastomosis in five cases. In cases where the diagnosis as to the type of portal hypertension cannot be established by clinical and laboratory means, it is probably advisable to proceed surgically with the plan of doing a splenorenal anastomosis. This shunting procedure should be of considerable benefit to patients with either type of portal hypertension.

#### SUMMARY

An attempt has been made to simplify the technical procedure of portacaval anastomosis and thereby eliminate some of its hazards. Two objections to the use of a direct suture anastomosis have been overcome. Adequate exposure has been obtained and the inferior vena cava has been occluded only partially. Suture anastomosis resulted in thrombosis in only one of fifteen animals.

The right thoracoabdominal approach described provided excellent exposure of the inferior vena cava and portal vein, and greatly facilitated the performance of the anastomosis. The use of a left thoracoabdominal approach for splenorenal anastomosis in clinically doubtful cases is suggested.

The operation in two dogs of this series was performed by Spencer T. Chester, M.D.

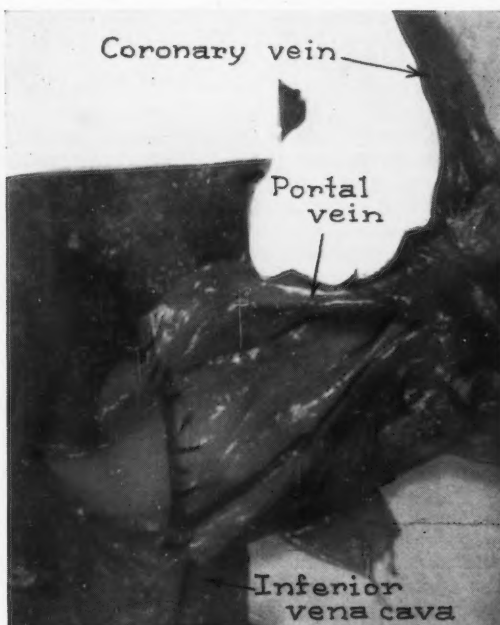


Figure 5.—Photograph of specimen obtained at necropsy five days after portacaval anastomosis.\*

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\* The authors wish to express their thanks to Dr. Robert O. Holmes of the Department of Pathology, University of California Hospital, for the photograph of this specimen.



## Streptomycin Therapy of Tuberculosis

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SINCE the first report of the inhibitory action of streptomycin against *Mycobacterium tuberculosis* in January, 1944, interest in the clinical use of this antimicrobial agent in tuberculosis has become increasingly widespread. In a disease as prevalent as tuberculosis there is inevitably a great demand for any therapeutic agent which might possibly be of benefit. In some forms of tuberculosis the response to streptomycin therapy has been dramatic, and in others the response has been superior to that elicited by previous types of treatment. Yet in many forms of tuberculosis results have not been encouraging. Clinical experience is still too limited to allow determination of the final role of streptomycin in the therapy of tuberculosis; this must await the outcome of extensive cooperative investigations now being carried out in various parts of the world.

During the interim period of evaluation, efficient utilization of the drug depends on application of the pharmacologic and therapeutic principles thus far determined. It is the purpose of this review to summarize some pertinent aspects of the pharmacology of streptomycin and to review the current medical literature on the treatment of tuberculosis with this drug.

Streptomycin was originally discovered in January, 1944, by Schatz, Bugie and Waksman<sup>30</sup> and was demonstrated to inhibit the growth of tubercle bacilli in vitro.<sup>30,31</sup> It was then shown to have an inhibitory influence on tuberculous infection in guinea pigs by Feldman, Hinshaw and Mann<sup>14,15</sup> and in mice by Youmans and McCarter.<sup>36,37</sup> The first cases in which tuberculosis in human beings was treated with streptomycin were reported by Hinshaw and Feldman in September, 1945,<sup>19</sup> and by November, 1946, they had treated 100 patients.<sup>29</sup> Numerous reports of treatment of patients have appeared in the literature during the past year, and in November, 1947, a combined report by the Veterans Administration, Army and Navy summarized experience in 543 cases.<sup>8</sup>

### PHARMACOLOGY

**Absorption.**—Parenteral injection is the usual method of administration of streptomycin, the intramuscular route being the most common. Fifteen minutes after a single intravenous injection of 600 mg. the concentration in the blood is from 30 to 35 micrograms per cubic centimeter.<sup>41</sup> The concentration decreases over a period of six hours to about 5 micrograms per cubic centimeter. With a single intramuscular injection of the same amount the maximal concentration in the blood is not as high as with a single intravenous injection, but the concentration is maintained at slightly higher levels over the six-hour period. Continuous intravenous infusion of 3 gm. per day produces concentrations in the blood

varying between 20 and 60 micrograms per cubic centimeter. The same total daily dose (3 gm.) given in eight divided intramuscular injections at three-hour intervals produces similar concentrations of between 30 and 60 micrograms per cubic centimeter of blood. Intramuscular administration of 1 gm. daily produces concentrations in the blood varying between 10 and 20 micrograms per cubic centimeter.

Oral administration of 1 gm. daily does not produce significant concentrations in the blood. This is due not primarily to destruction of the drug by digestive enzymes, but rather to poor absorption. Animal experiments<sup>29</sup> have shown that adequate concentrations in the blood can be obtained if a sufficient quantity of the drug is administered by mouth. This quantity is about 30 times the parenteral dose.

When streptomycin is administered intrathecally there is good retention of the drug within the cerebrospinal fluid. Administration of from 15 to 20 mg. results in concentrations of from 13 to 25 micrograms per cubic centimeter of cerebrospinal fluid 24 hours later.<sup>6</sup>

Administration of streptomycin by nebulization in daily doses of 500 mg. does not result in significant concentration in the blood.<sup>18</sup>

**Distribution.**—When patients with no meningeal infection are given from 1 to 3 gm. of streptomycin daily with resultant concentrations of from 13 to 27 micrograms per cubic centimeter of blood, the concentration in the spinal fluid is from 1 to 5 micrograms per cubic centimeter, thus demonstrating that streptomycin is poorly absorbed into the cerebrospinal fluid in the presence of the normal blood-brain barrier.<sup>41</sup> However, when patients with meningeal infection and, hence, with a change in the blood-brain barrier, are given the same dose, higher concentrations in the cerebrospinal fluid are obtained.<sup>1,41</sup>

The amount of streptomycin in pleural fluid varies from patient to patient.<sup>1,6</sup> The concentration obtained is probably dependent upon the presence and type of inflammation of the pleura. Higher concentrations might be expected in pleural effusion secondary to constrictive pericarditis than in chronic empyema in which the pleura is thick and fibrotic.

Appreciable concentrations are obtained in peritoneal fluid in cases of peritonitis and of ascites.<sup>6</sup>

Streptomycin diffuses into the intra-ocular fluids.<sup>41</sup>

The distribution of streptomycin in the tissues and organs of the body has not been fully investigated. Data obtained from two postmortem examinations showed that most of the detectable drug was in the blood serum, kidney and bile in the gallbladder.<sup>1</sup> Small amounts were present in the lungs and heart muscle. Negligible amounts were found in the brain and liver. Low concentrations in the liver and spleen have also been demonstrated in mice.<sup>27</sup>

Streptomycin is transmitted through the placenta into the fetal blood.<sup>18,35,41</sup> Therefore, the same (or

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greater?) potentialities for toxicity are present in the fetus as in the mother.

**Excretion.**—The major excretory route of streptomycin is through the kidneys, and approximately two-thirds of the administered drug may be recovered in the urine within 24 hours.<sup>41</sup> The rate of excretion varies with urinary output, and the excretion is apparently accomplished by glomerular filtration.<sup>1</sup> A small amount (2 to 5 per cent) is excreted in the bile.<sup>18, 41</sup>

About 2 per cent of a dose administered parenterally can be recovered from the feces.<sup>41</sup> This may represent biliary rather than bowel excretion. After oral administration most of the drug can be recovered from the feces.

Secretions from the tracheobronchial tree contain appreciable concentrations of streptomycin after parenteral administration of the drug.<sup>32</sup>

**Toxicity.**—Histamine reaction: The earlier preparations of streptomycin contained a histamine-like substance which produced flushing, headache and fall in blood pressure. Commercially available streptomycin is now so prepared that this reaction does not occur.

**Local irritation:** Intramuscular injection of streptomycin may produce soreness and induration at the site of injection. The irritation is caused mainly by impurities rather than by the antibacterial agent, and as more highly purified streptomycin is appearing on the market, this reaction is being encountered less frequently.<sup>23</sup> The discomfort can usually be controlled by applications of heat or cold or by adding a 1 per cent solution of procaine hydrochloride to the streptomycin solution.

Although most patients tolerate the daily instillation of from 50 to 100 mg. of streptomycin intrathecally, the drug produces definite irritation of the meninges. The severity of this irritation is roughly proportional to the total dose and is greater when less highly purified streptomycin is used.<sup>23</sup> Even when the dose is from 10 to 20 mg., pleocytosis commonly occurs.<sup>6</sup> Rarely, there are symptoms of this meningeal irritation. Some individuals complain of pain over the sacrum lasting for from 12 to 24 hours after the intrathecal injection.<sup>23</sup> In prolonged courses this reaction usually disappears after one or two weeks. As much as 275 mg. administered intrathecally once daily for several weeks has been tolerated by some patients, but many patients have reactions to this high dose.<sup>13</sup> The reaction occurs in less than one hour and consists of headache, vomiting and nystagmus. The patient becomes somnolent and respirations slow, and there may be urinary retention. The reaction gradually subsides in the course of 48 hours. Administration of a 1 per cent solution into the pleural and peritoneal cavities has been well tolerated.<sup>23</sup>

**Hypersensitivity:** Various manifestations of hypersensitivity may occur during streptomycin therapy.<sup>13, 23</sup> Occasionally the patient's temperature will rise to from 102° to 104° F., five to seven days after the beginning of a course of the drug. In approxi-

mately 5 per cent of patients dermatitis occurs. The dermatitis resembles the common forms of drug rash and may be associated with eosinophilia and constitutional symptoms of varying severity. Rarely, exfoliative dermatitis may appear. In a large proportion of patients eosinophilia will develop either with or without dermatitis during prolonged courses of treatment with the drug. These allergic reactions seldom give cause for permanently discontinuing therapy. However, since the relationship of drug hypersensitivity to diffuse vascular disease is not clearly understood, such reactions may possibly carry long-term serious potentialities.

**Renal toxicity:** Often cylindruria and occasionally albuminuria occur unassociated with hematuria or nitrogen retention. These conditions are apparently of no significant consequence and may be minimized or eliminated by alkalization of the urine.<sup>13, 23</sup>

In a small proportion of patients definite reduction in renal function develops, as evidenced by a decrease in the result of the urea clearance test and rise in concentration of blood urea nitrogen. This reduction in function may be an advanced form of the same process which produces the benign cylindruria, but its exact relationship to the cylindruria is not known.<sup>23</sup> In almost all instances it has occurred in patients who had renal disease prior to streptomycin therapy. It has not been established whether alkalization of the urine will prevent the development of this condition, but for the present such a precaution seems warranted.

**Neurotoxicity:** In almost all patients receiving streptomycin in prolonged courses and in large doses, damage to vestibular function will develop.<sup>8</sup> If administration of the drug is continued, this reaction leads to complete and presumably irreversible loss of vestibular function in the majority of cases. The onset occurs at the end of about the fourth week of therapy with doses of from 1 to 2 gm. daily and at about the end of the third week with doses of 3 gm. daily.<sup>23</sup> Often the first sign is a headache which subsides in 24 hours. The patient then notes the onset of dizziness. This is not true vertigo, as the rotary component is lacking. The sensation is accentuated by movement, and the patient has a sense of "overshooting the mark," although the past-pointing phenomenon cannot be demonstrated. Sometimes nausea and, rarely, vomiting occur. The acute symptoms last for approximately seven to ten days, after which the patient begins to learn to compensate for the lost vestibular function. The degree and rapidity of development of compensation vary from patient to patient, and older persons have a poorer ability to compensate. Patients may experience difficulty in walking in the dark after compensation has taken place, but accommodation is usually good in from 60 to 90 days. While the loss of vestibular function is not of serious import to the average patient in comparison with the disease for which streptomycin is being administered, it is conceivable that it would have a profound effect on patients who are blind or who have disease of the posterior columns or cerebellum.

Under certain conditions, use of streptomycin will

cause nerve deafness.<sup>23</sup> However, this deafness is not a common occurrence. It has been reported to occur (1) during intrathecal therapy for meningitis, (2) during prolonged intramuscular therapy with excessive doses (4 to 10 gm. per day) and (3) in the presence of renal insufficiency with retention of excessive concentrations of streptomycin in the blood. It has been reported that the first sign of impending cochlear damage is a low-pitched continuous roaring tinnitus.<sup>5</sup> Discontinuance of use of the drug when the tinnitus begins would probably prevent significant auditory loss. In a few instances, when there has been definite but incomplete auditory loss, discontinuance of use of the drug has revealed that this loss is partially reversible. Continuance of streptomycin therapy may result in complete deafness.

The site of the lesion causing these neurologic abnormalities is not known with certainty at present, but there is limited evidence that liquefaction necrosis of the vestibular and cochlear nuclei is involved.<sup>23</sup>

**Blood dyscrasias:** Eight instances of blood dyscrasias occurring in association with streptomycin therapy have been reported.<sup>8</sup> Five of these consisted of mild leukopenia with neutropenia and the other three consisted of agranulocytosis. Thrombocytopenia may occur rarely.<sup>9</sup>

**Dosage and route of administration.**—Intramuscular: The results of investigation of the optimal dose of streptomycin are just beginning to appear in the medical literature. Until recently a policy of giving as large doses as possible without invoking symptoms of major toxicity has been followed by many clinicians. Presumably the upper limit of reasonable tolerance is about 3 gm. daily, and 2 to 3 gm. daily has been a commonly utilized dose. However, the incidence of vestibular nerve damage from use of these large doses has been very high (96 per cent of 543 patients receiving 2 gm. daily for 120 days),<sup>8</sup> and investigations have been undertaken to evaluate lower dose schedules. Although reports of this work have not as yet been published, an editorial resume in *The Journal of the American Medical Association*<sup>12</sup> announced encouraging preliminary results. Therapeutic effects of the use of 1 gm. daily were similar to those produced by use of 2 gm. and the incidence of vestibular toxicity was reduced to about 20 per cent. The frequency of appearance of predominantly resistant organisms was not altered.

The frequency of injection is also undergoing change as a result of recent investigations. Formerly, the daily dose had been divided into four to eight portions and administered at three to six-hour intervals in an effort to maintain a reasonably constant concentration in the blood. Feldman, Hinshaw and Karlson<sup>16</sup> demonstrated that division of the daily dose into two portions and administration at 12-hour intervals was as effective in inhibiting tuberculous infection in animals as administration at shorter intervals. Preliminary studies<sup>12</sup> in man with doses of 0.5 gm. every 12 hours apparently affirmed the therapeutic effectiveness and showed that toxicity is not increased. There is experimental evidence<sup>11</sup> that tuberculous infection in guinea pigs may be maximally

inhibited by one injection of streptomycin every five days and partially inhibited by one injection every ten days. It thus appears likely that the maintenance of a constant concentration of streptomycin in the blood will not prove to be necessary and that the drug will be administered less frequently than it is now.

The duration of effective intramuscular therapy is limited by the frequent occurrence of bacterial resistance. Cultures in nearly all cases may be expected to exhibit predominantly resistant organisms after 120 days of streptomycin therapy. Although patients are commonly treated for from 90 to 120 days, investigation of shorter schedules is now under way.<sup>24,26</sup>

**Inhalation:** When streptomycin is administered by inhalation of a nebulized solution, the commonly used daily dose is 500 mg., dissolved in 10 cc. of physiologic saline solution and given in 5 to 10 portions.

**Intrathecal:** The optimal intrathecal dose in tuberculous meningitis has not been determined. A daily injection of 100 mg. has been used frequently, but it more recently has been suggested that 50 mg. is a preferable dose.<sup>12</sup> Intrathecal injections are usually administered every one or two days. Specific data concerning the optimal duration of intrathecal therapy in tuberculous meningitis have not been reported. Persistent return of the concentration of sugar in the spinal fluid to a normal figure might or might not be a logical guide.

It should be emphasized that the therapeutic results cited in a subsequent section of this paper have been obtained with intramuscular and intrathecal doses larger than the currently advocated amounts. In summary, in the treatment of tuberculosis the present recommendation<sup>12</sup> is that 0.5 gm. of streptomycin be given intramuscularly every 12 hours for 120 days, except in cases of miliary and meningitic tuberculosis, when use of 2.0 gm. or more is advised. In meningitis the intrathecal injection of 50 mg. every one or two days is also recommended.

**Action.**—Almost all strains of tubercle bacilli, isolated in cases of tuberculosis in which the patients have never received streptomycin therapy, have been predominantly sensitive to the antimicrobial effect of streptomycin.<sup>25,38</sup> The bacteriostatic concentration in vitro was found to be 1.56 micrograms or less per cubic centimeter in 90 per cent of a series of 131 strains, and the majority of the organisms were sensitive in a concentration of 1 microgram or less per cubic centimeter.<sup>38</sup> The bactericidal concentration has been shown to be in excess of 50 micrograms per cubic centimeter.<sup>39</sup> Thus it can be seen that the concentration obtained in the blood of most patients is well in excess of the bacteriostatic concentration but is not bactericidal.

Bovine strains of tubercle bacilli are comparable to human strains in their susceptibility to streptomycin in vitro<sup>38</sup> and in vivo.<sup>17</sup>

Although cultures made prior to streptomycin therapy show predominant sensitivity to streptomycin, cultures made after treatment very frequently show predominant resistance to the antimicrobial



action of the drug. Cultures of tubercle bacilli have been shown to become resistant to streptomycin both *in vitro*<sup>25,34</sup> and *in vivo*.<sup>38,40</sup> This is one of the major limiting factors of its use in the treatment of tuberculosis. In one series, resistance was observed as early as the 35th day of therapy and occurred in 19 of 20 patients after from 90 to 120 days.<sup>8</sup> In another series it developed in 39 of 62 patients after from 60 to 120 days.<sup>8</sup> Whether the isolation of resistant organisms indicates that further streptomycin therapy will be ineffective in a particular case has not been determined without doubt, but available evidence strongly favors this view.<sup>24,26</sup> The resistance which develops is apparently of long duration, if not permanent, and is retained after numerous subcultures and passage through guinea pigs.<sup>22</sup> A study by Pyle<sup>28</sup> indicated that "strains" of tubercle bacilli isolated from patients before streptomycin therapy may contain small numbers of resistant organisms, although the "strains" are predominantly sensitive to streptomycin. This suggests that streptomycin therapy, by inhibiting the sensitive members of the strain, allows the more resistant members to flourish and eventually to become predominant. It seems likely that other mechanisms also are involved in the development of bacterial resistance to streptomycin.

#### CLINICAL USE

Since streptomycin does not have a uniform effect in the several types of tuberculous infection, the reported results of therapy will be discussed under various disease types.

**Primary phase tuberculosis.**—No extensive reports of treatment of the primary phase are available. In view of the favorable prognosis presented by a proper conservative regimen of therapy, streptomycin apparently has no place in the treatment of this type of infection at present.

**Reinfection phase pulmonary tuberculosis.**—Minimal pulmonary tuberculosis: The prognosis in cases of minimal reinfection with use of adequate bed rest and collapse therapy, when indicated, is favorable in at least 90 per cent of cases. In view of the hazards of toxicity and of the development of bacterial resistance, streptomycin is not recommended as an initial form of treatment.

Moderately and far advanced pulmonary tuberculosis: In this condition cavities may be thick walled, the structure and physiology of the lung may be altered by fibrosis, and vascularity in many of the diseased areas may be diminished. It might be expected that a bacteriostatic agent would have limited value in significantly affecting a disease in which these conditions are present.

In a carefully studied series of 157 cases<sup>8</sup> it was demonstrated that streptomycin therapy had little effect on old fibrous or caseous lesions but was associated with improvement in the majority of exudative lesions. Although exudative lesions frequently exhibited striking regression, resolution of these lesions was rarely complete, and relapse after completion of treatment was frequent.

Hinshaw and his associates<sup>21</sup> did not recommend employing streptomycin in the treatment of chronic fibrocavicular pulmonary tuberculosis unless conspicuous evidence of recent exudative disease is found. They also emphasized that streptomycin has little to offer if the rapidly progressing exudative lesions are merely part of a terminal phase of overwhelming infection.

Muschenheim and his colleagues,<sup>26</sup> in a study of 43 patients, also found that exudative pulmonary tuberculosis responded more favorably to streptomycin therapy than fibrocavicular disease. Although the incidence of sustained satisfactory remission was not high, less complete improvement sometimes allowed surgical collapse in cases not suitable for such measures before streptomycin treatment.

**Tuberculous empyema:** After intramuscular administration, usually concentrations of streptomycin in empyema fluid are reasonably high. However, the results of parenteral treatment or of instillation of streptomycin into the pleural cavity are not encouraging. Hinshaw, Feldman and Pfuetze<sup>20</sup> reported that improvement occurred in one of seven cases and suggested both the acidity of the empyema fluid and the granulomatous nature of the disease as being unfavorable factors.

**Bronchogenic dissemination.**—Recent pulmonary spreads: Favorable results of treatment of these lesions were reported by Hinshaw, Pyle and Feldman,<sup>21</sup> by Canada,<sup>7</sup> and by Muschenheim and his colleagues.<sup>26</sup> As the pathologic process is usually exudative, streptomycin may prove of value when resolution does not take place under conservative therapy.

**Tuberculous tracheobronchitis:** Brewer and Bogen<sup>3</sup> reported a series of 44 cases of ulceration and granulation of the trachea and bronchi. They divided these into several groups and employed streptomycin by aerosol and in various doses intramuscularly. Aerosol therapy (500 mg. daily) alone and intramuscular injection of 0.5 gm. and 1.0 gm. respectively, daily were partially effective, while intramuscular injection (2.0 gm.) alone and intramuscular injection in combination with aerosol therapy were each effective in 13 cases.

**Tuberculous laryngitis:** Black and Bogen,<sup>2</sup> and Hinshaw, Pyle and Feldman<sup>21</sup> reported favorable results in the treatment of this condition. In 34 cases<sup>2</sup> in which varying doses and varying routes of administration were used, lesions healed in 13, improved in 17 and were unimproved or worse in four. These results were definitely superior to those achieved in similar cases with former methods of therapy.

**Hematogenous dissemination.**—Acute generalized hematogenous dissemination (miliary tuberculosis): Arrest of miliary tuberculosis in several isolated instances has been reported, and there is no doubt of the therapeutic effect of streptomycin on this type of infection. However, study of large series of cases revealed that the disease still carries a very significant mortality rate.<sup>8,24</sup> The major causes of failure of streptomycin therapy in this instance are the develop-

ment of bacterial resistance to streptomycin and the occurrence of a complicating tuberculous meningitis during therapy. Until prolonged follow-up studies have been completed, the incidence of recurrence and the ultimate mortality rate in cases of streptomycin-treated miliary tuberculosis cannot be determined. However, present evidence suggests that the mortality rate is significantly reduced by use of the drug.

**Tuberculous meningitis:** A number of apparent arrests of this condition due to streptomycin have been reported. Arrest of this type of tuberculosis presents a striking demonstration of the influence of this antibiotic agent on tuberculous infection. However, the effect of such treatment on the ultimate mortality rate of the disease has not yet been determined. That the effect will not be as favorable as that in miliary tuberculosis without meningeal involvement is generally conceded; and that use of streptomycin will alter an eventually fatal outcome has been doubted by some investigators.<sup>8</sup> In a series of 91 cases of tuberculous meningitis in which the drug was used,<sup>8</sup> 58 of the patients died, and at the time of the report in only 18 of the remaining 33 cases had treatment been completed and the infection apparently arrested. The percentage of these 18 cases in which relapse may be expected to occur is unknown. The intrathecal, as well as the intramuscular, route of administration has been strongly advocated in this disease. Although in cases of meningitis significant concentration of the drug in the spinal fluid is obtained by intramuscular administration, intrathecal administration produces a concentration which may be bactericidal rather than only bacteriostatic. It is desirable to decrease meningeal infection as rapidly as possible, for prolonged inflammation will produce lesions mechanically incompatible with life, even though bacteriostasis is eventually obtained.

**Osseous tuberculosis:** Satisfactory response to streptomycin therapy of this condition was noted by Hinshaw, Feldman and Pfuetze,<sup>20</sup> but others have reported less satisfactory results.<sup>8</sup> We have observed two patients with single osseous lesions which regressed strikingly during streptomycin therapy. It is anticipated that results with this type of infection will be variable.

**Tuberculous lymphadenitis:** The results of treatment of enlarged tuberculous nodes are variable.

**Genito-urinary tuberculosis:** Cook, Greene and Hinshaw<sup>10</sup> and Hinshaw, Feldman and Pfuetze<sup>20</sup> reported the results of treatment in 15 cases of renal tuberculosis with tuberculous cystitis. They noted marked symptomatic improvement in 50 per cent of cases and a reduction in the degree of bacilluria in the majority. However, return of symptoms and bacilluria was a frequent occurrence, and they felt that use of streptomycin was palliative rather than curative. It has been emphasized that streptomycin therapy is not a substitute for nephrectomy in cases of unilateral renal tuberculosis.

**Tuberculous enteritis.**—There is, as yet, no basis for defining the place of streptomycin in the treatment of enteric tuberculosis. Final evaluation of treatment will be difficult, since antemortem diag-

nosis of this condition may be uncertain. Sweany noted marked symptomatic improvement in a few cases.<sup>33</sup>

**Tuberculous sinus tracts.**—Sinuses originating in bone or lymph node and fistulae originating in the gastro-intestinal tract are strikingly affected by streptomycin. Brock<sup>4</sup> reported closure of 59 of 60 sinuses (12 patients) and emphasized the importance of establishing surgical drainage whenever indicated. It is frequently necessary to carry out debridement of necrotic bone and similar procedures to obtain maximal benefit.

**Miscellaneous tuberculous infections.**—Few cases of streptomycin therapy in tuberculous pericarditis, peritonitis, dermatitis, ocular lesions and other tuberculous complications have been reported. After use of streptomycin, improvement has been noted in some of these extrapulmonary lesions.<sup>8,20</sup>

**Adjunct to surgical treatment of tuberculous lesions.**—Since streptomycin therapy has shown promise in cases of recent spread of pulmonary tuberculosis, there is a rationale for preoperative and postoperative administration of the drug in cases of tuberculosis in which thoracoplasty, lobectomy or other such procedures are performed. It might be hoped to reduce the incidence of contralateral spread and tuberculous empyema after operation. Evaluation of this adjunctive therapy will take place as an increasing number of patients are studied.

#### SUMMARY

On the basis of these reports there appear to be indications for streptomycin therapy in the following conditions: laryngeal and endobronchial tuberculosis, miliary tuberculosis, tuberculous meningitis, osseous tuberculosis, tuberculous lymphadenitis, sinuses and fistulae, and exudative tuberculous pulmonary lesions not responsive to conservative therapy. In genito-urinary tuberculosis and tuberculous enteritis, streptomycin may have a place in treatment as a palliative medication.

It is desirable for the present time to limit the use of streptomycin to these types of tuberculosis for the following reasons: First, streptomycin is a definitely toxic drug. When the disease process is severe, the prognosis grave, and use of streptomycin indicated, the toxicity hazard is not comparatively great, but when the disease process can be controlled by other measures or when streptomycin has shown little promise in similar cases, the toxicity hazard cannot be taken lightly. Secondly, after a prolonged course of treatment with streptomycin, strains of tubercle bacilli frequently appear which are resistant to streptomycin. This resistance is prolonged and a return of sensitivity has not been reported. Therefore, after one course of streptomycin therapy the drug may become and remain totally ineffective and hence may be useless at a later date when the indication for its use is more urgent.

It should be emphasized that streptomycin is merely an adjunct to the treatment of tuberculosis. In the concentrations obtained in the blood, the drug is only bacteriostatic. The actual killing of tubercle bacilli and healing of lesions must be accomplished



by the immune mechanisms of the body, and the patient should be given all the supportive measures of modern tuberculosis therapy. Bed rest, careful dietary supervision, skilled nursing care, collapse procedures as indicated, symptomatic medication, all are necessary to obtain maximal benefit from streptomycin therapy.

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## The Physician's Point of View on Regional Organization of Hospitals

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IT was with reluctance that I accepted the invitation to speak to you today concerning the attitude of the medical profession toward the planning of regional organization of hospital services. As far as I am aware approval of a definite plan for this purpose has not been made by the American Medical Association or any state medical association with one possible exception. Approval may have been granted to local plans by local societies but if so I am not cognizant of it.

The matter has not been widely discussed in state associations or in the American Medical Association. My opinions must therefore be based upon a wide acquaintanceship with physicians in all parts of the country and a knowledge of their reactions. Long contact with local, state, and national organizations furnishes a basis of estimating the opinion of these bodies.

It seems likely that my remarks will not be pleasing to some of you. From an analysis of the information at my disposal concerning regional organization it appears that there are in reality three phases to such plans. These involve the functions limited to hospitals themselves, staff functions, and an intermediate area where one impinges upon the other.

The medical profession has a right to expect that hospitals exercise the functions peculiar to them in such a manner that the hospital will be efficiently and properly operated. Only in this way can the physician be assured of a satisfactory place in which to care for his patients who require hospitalization. The methods and details concerned with the achievement of this end are outside the province of the physician.

It is recognized that the governing authority of the hospital is in most instances responsible for the appointment of the staff and the administrative personnel of the institution. After the staff has been created it must be autonomous in exercise of its functions. It must not be interfered with by either the governing body or the administration, provided it performs its duties in a way which fulfills the requirements of competency and ethics.

The intermediate area in which hospital and staff functions overlap is the most fruitful source of conflict and misunderstanding. Certain facilities have grown up about hospitals which involve the activities of medical personnel and the practice of medicine. Hospitals tend to look upon these as lying in the legitimate sphere of hospital activity. The medical profession tends to look upon them as an invasion of the practice of medicine. In certain instances this is clearly the case and in many states some of these activities certainly constitute a violation of the law.

In the majority of instances a reasonable adjustment between physician and hospital exists but

neither party is entirely satisfied. There are practical problems which stand in the way of a satisfactory solution. Time, patience, and a mutual desire to cooperate on a reasonable basis are required of both parties if an agreeable arrangement is to be achieved. An arbitrary and uncompromising approach by either will delay or even jeopardize a proper solution.

The physician has a natural concern about all matters affecting hospitals because these necessarily involve his interests and those of his patients. He will, therefore, carefully scrutinize any program designed to change the status of hospitals. He will be on the alert for signs of an increased tendency to infringe upon his field and for any move to limit the freedom of hospitals or the profession.

As I understand the regional organization plans proposed they envision the division of hospital facilities into four groups.

1. The hub of the plan is a teaching center, consisting of a medical school and a hospital of two hundred or more beds. It would have all the facilities usually found in a medical school and a teaching hospital.

2. The intermediate or regional hospital of one hundred to two hundred beds. It would be organized with services staffed by recognized specialists but would lack research and certain teaching facilities.

3. Rural hospitals of fifty to one hundred beds equipped to care for ordinary illness.

4. Community health and medical care centers with offices for physicians and a few beds for minor illness, emergencies and "normal obstetrical cases."

It is contemplated to organize these institutions into an integrated plan which would assign certain functions and duties to each and limit them in some degree in their scopes of activity.

There is no positive statement as to who would construct the new institutions which would be necessary to such a program. There is a suggestion that finances would be derived from tax sources. The assumption is that local, state, and federal funds would be used. There are statements that existing facilities would join together under the plan on a voluntary basis. The mechanism of control of new and old facilities is not entirely clear.

It has been stated that hospitals in this country have developed on the basis of community wealth or individual benefaction rather than in response to population need. There is some truth in this statement but it does not present an accurate picture of the hospital situation in California. The present distribution of hospital beds does not reflect current needs, but one must take into account the fact that construction during the war years was almost impossible and is still expensive and difficult.

There is at present, and for many years there has been, an informal relationship between physicians, and, in some instances, between physicians and hos-

pitals, resulting in a degree of differentiation of the types of cases treated in the facilities of local communities. There has been a tendency for doctors in rural areas, small centers of population, and even sizable cities to refer patients who were gravely ill or had complicated problems to more skillful colleagues working in better equipped institutions. This practice is not uniform and is influenced by the attitudes of the patients and the physicians. It is often determined by the competency of the local doctor and the adequacy of existing facilities.

At this point it would be well to inquire what is to be gained by a program of regional organization. It is also pertinent to ask what disadvantages it might have and how feasible it is of attainment.

The advantages claimed for it are:

1. It would "decentralize or spread out from the largest cities into the remotest hamlet all the benefits modern medicine has to offer."

2. "Small hospitals can benefit by being able to look toward the larger district hospitals for consultation service, and when necessary, can refer patients to it. Patients might even be transferred directly to the base hospital if the particular case so indicated."

3. It would bring about "the flow of professional personnel and special services from the large hospital to the small one" and "the flow of patients, specimens and records from the small to the large institutions."

4. Consultations by specialists in medical fields and advice of technical hospital experts would be furnished by the larger to the smaller hospitals.

5. The larger hospitals would train personnel to staff smaller hospitals.

6. There could be certain economies effected by pooled purchasing by groups of hospitals.

Are these real advantages? The technical fields of hospital administration are without the scope of the medical man. I shall not comment upon them, except to remark that the interchange indicated exists in some degree now and can be developed to any desirable extent without formal organization.

With reference to "decentralization" of medical care and the extension of the benefits of modern medicine to the "remotest hamlet," I would raise the question whether the reverse might not be accomplished. Would there not be a tendency toward centralization? Certainly there is central planning and there would be central direction. To make a plan such as this work would require central authority. It is apparently planned to have certain patients and patients with certain diseases cared for in certain institutions. This would necessitate promulgation of rules and regulations. The outlined plan for consultants and advisors would tend to set and enforce the pattern of conduct of smaller institutions.

Is this not an unwarranted interference with the freedom of the patient, the physician and the hospital? It suggests an effort at regimentation. It also suggests the entrance of public health departments into the practice of medicine even in the most remote rural areas.

It is claimed that the smaller hospital could look toward the larger one "for consultation service" and

when necessary refer patients to it. The term "consultation service" obviously refers to medical consultation.

I would like to inquire how a hospital may know when a consultation is desirable or necessary and how a hospital may furnish a consultation. I have a firm conviction, which I believe is shared by practically all physicians, that the care of the patient, the decision as to need for consultation, the choice of the consultant and the furnishing of consultation constitute the practice of medicine and are solely and completely the function of the physician, with the consent of the patient.

By the same token, how can a hospital refer patients to another hospital? In the sense of medical care, a hospital has no patients. Persons confined to a hospital because of illness or injury are the patients of the physicians rendering care to them. It would be presumptuous for an institution lacking all the qualifications for the practice of medicine to consider that it has any function in this regard. In only an occasional instance, and then only by the staff rather than the hospital, should a demand be made upon a physician to obtain consultation.

The same is true of the designed "flow of personnel" and services except as these refer to the functions peculiar to the hospital as distinct from medical fields. The hospital is likewise exceeding its prerogative if it presumes to direct the flow of patients and specimens from one institution to another. Who is responsible for the care of the patient and the examination of specimens? It is not the duty or privilege of the hospital to do these things. These are acts which can be performed only by the doctor of medicine.

It is probable that words have been loosely used in explaining this program and the intent is not that expressed. Words, however, have certain meaning. The whole field of semantics has developed about this fact. When expressions implying interference with the practice of medicine are employed it is not unnatural that the medical profession would question the intention and effect of the program.

When the foregoing statements are coupled with the fact that certain institutions engage in the practice of medicine and some hospital administrators have openly proposed that physicians be employed by hospitals to practice their profession on a salary basis, the element of suspicion in the minds of doctors is increased many fold. Let us have a frank and accurate statement of the intentions of the hospitals and program of regional organization. Unless this is done and the statement is satisfactory, not only will there be a lack of cooperation but there will be strong opposition on the part of the medical profession.

I have reviewed the plans for regional organization of hospitals for California and Michigan. Both resemble tables of operations of military organizations. To place them in full operation would require corresponding military discipline. This is found in civilian life only in the authoritarian state. Certainly none of us wishes that. It could be directly accom-



plished only by changes in the basic law of the country which would make the hospitals and the physicians subject to direction by governmental authority.

There are more insidious, indirect methods which could be employed to accomplish similar ends. The dispensation of government funds is the usual means of forcing people or organizations into the acceptance of dictation. Funds could be, and in fact are, made available only to institutions conforming to certain rules laid down by those who dispense the funds. Reasonable conformity to standards of construction and operation cannot be objected to but it could be a short step from this requirement to acquiescence in control and operation.

There is also the possibility that some units of government might build hospitals to be operated in competition with existing facilities. You may believe this remote. I hope it is, but I would call your attention to the rapid increase in veterans' hospitals, public ownership of certain hospitals not designed for mental or communicable diseases, the perversion of some of our county hospitals and the determined assault upon the means test. It is not beyond the realm of possibility, and should it occur it would sound the death knell of private hospitals and the freedom of medicine.

You, as hospital people, are in a much better position than I to know, but it is my impression that private hospitals are operated upon a more efficient and economical basis than are corresponding public institutions. In those with which I am acquainted it is true.

It is my opinion, which I believe is almost universal among physicians, that with the exception of care of indigents, persons with mental or communicable disease, and certain other classes of individuals, government has no place in the field of hospitalization.

A hazard is ever present in the use of government funds for hospital construction. As yet this has not involved control, but funds can be obtained only by compliance with rigid regulations which at times may be unreasonable. The old adage that "he who pays the piper calls the tune" is still true. The greater the utilization of tax funds from federal or other sources, the greater will be the measure of governmental control.

The bureaucrats with their expanding desire for power will not be content to sit idly by and watch uncontrolled grants-in-aid continue. They inevitably will strive to extend their control under the guise of beneficent regulations.

The politicians have not refrained from interference in hospitals for indigents and those for special classes of patients. Consider the great temptation to control the affairs of institutions designed for paying patients.

Let us now return to the planning of regional organization. The community health and medical center is supposed to be flexible in size and form. In smaller areas it is contemplated to staff it at intervals with visiting teams. It is a place in which "preven-

tive" services are to be found along with medical care for illness. Where does one draw the line between the two? How are these services to be provided? Could this arrangement not become an opening wedge for the extension of the activities of public health departments into the practice of medicine? We are in need of a clear delineation of the proper functions of public health departments, a limit beyond which they should not and cannot go in the field of medical care.

The larger center is designed for the care of emergencies, ordinary illness, and "normal obstetrics." Is this a practical arrangement? How grave is an emergency and what preparation is necessary for its care? Is the prospective mother whose labor is interrupted or whose placenta separates prematurely to be submitted to cesarean section at the center, or to be transported a considerable distance while in a serious condition? Who is to make these decisions—the administration, some higher authority, or the physician? Would it not be wiser to plan for obstetrical care in a better-equipped facility?

The rights, powers, and duties of the board of controlling authority and the administrator of the hospital are described in some detail. Nowhere do I find the practice of medicine defined. The physician is charged with duties but enumeration of his rights and powers is omitted. Is this omission the result of intent or oversight? If the latter, does it indicate a philosophy of relegating the physician to a secondary status?

It is stated, "Ideally, it would appear that the hospital is the logical place to refer patients for all types of diagnostic procedure." I reiterate that diagnosis of disease constitutes the practice of medicine, an activity denied the hospital by law. Even if this were not true, one would be impelled to ask what basis is there for the belief that the hospital could provide a more accurate diagnosis than the practitioner of medicine and is it the intent of the hospital to displace the private physician?

"A well organized outpatient department should be an integral part of the hospital and the health service of the community" is another statement requiring scrutiny. There is no mention of a means test. The logical conclusion would be that it is recommended that the hospital foster an outpatient department to compete with the physician. This is again the practice of medicine.

Associated diagnostic clinics are advocated: "Employing the principle of group practice, they avoid duplication of equipment, save time of the attending physician, are more convenient for patients and permit more effective medical care." By and large, group practice does these things to an insignificant extent if at all. "Effective medical care" depends upon the abilities of the individual physician whether in a group or alone. I have no criticism of group practice for those who wish it. Certain physicians find it desirable for reasons which pertain to their own welfare. Others do not. It is presumption for a hospital, a state agency or other organization to tell physicians how their practices should be conducted. It is dis-

tinctly not in their province and to attempt to set up diagnostic clinics in the hospitals is again the invasion of the field of medicine unless these facilities are designed for indigents.

In the minds of the medical profession the hospital exists for the purpose of extending the scope of medical care. In fulfilling that purpose it is an independent allied service and is not and cannot be the dominating and directing force in medical care. After all, the physician sees many patients in his office or in the home for every patient he sees in the hospital.

An apparent attempt to limit the freedom of the physician is found in this statement: "The rules and regulations adopted by staffs and governing boards of small hospitals should be based upon facilities and indicate the limitation of medical practice within the institution." Any limitation of medical practice must be purely a staff function. One may ask what do boards of laymen know about the problem and by what right do they propose to adopt rules governing medical procedures. This idea shows a fundamental lack of understanding of medical care.

It disregards entirely the capabilities of individual staff members. I have taught medical students, interns and residents for years and have followed the careers of many as they have established practices in different communities. I know something of their abilities. I also participate in the examination of candidates for the American Board of Surgery, and in this way come in contact with men of ability who have had excellent training and who are practicing in various communities throughout the West. For some years I have served as a member of the Applicants Committee and the Credentials Committee of the American College of Surgeons for Northern California.

As a result I have examined the records of operations of men from all parts of this area. There are well trained and competent surgeons in communities too small for more than a rural hospital who are performing creditably and successfully practically all the procedures of general surgery. In some instances they possess abilities at least as great as their colleagues in nearby cities of greater size. Who is to gainsay men of this type? Certainly not a board of laymen.

Let us now consider the feasibility of this program. Without methods of force, it can be effective only to the degree the patient, the hospital and the physician wish to make it so.

The physician must determine which patient should be referred to another physician. He must also decide where and to whom the patient should be sent. The patient must make the decision as to whether he wishes his care to be rendered at home and by a local physician or elsewhere and by someone else. The freedom of the patient and the physician cannot be abridged. Neither will permit it.

The average physician is more concerned about the welfare of his patient than any other item. He knows his own limitations and the limitations of the facilities available to him. If he does not recognize these he can be dealt with on a local level but not by a statewide plan imposed from without.

Hospital cooperation is not within my scope but I doubt if many of you would be willing to bind your institutions to a plan which would circumscribe their functions and development. Certainly no one would suggest that a first-class hospital in a small community should be reduced in size or scope to meet a prearranged population pattern.

In such a program local civic pride will be encountered. Rivalry between neighboring communities is often intense. Population limitation on size, character and scope of hospitals will not generally be accepted by the citizens. This has already been demonstrated in California. Perhaps unwisely from an economic point of view some localities desire more extensive facilities than the State Department of Health believes justified.

Population growth varies and population shifts occur. Who can be sufficiently certain of the future to say with assurance that some of these communities may not be more wisely planning for their future needs than those who would prescribe arbitrary standards for them?

The medical profession is opposed to extending the regulation of the lives of individuals and their activities. The whole plan of regional organization is reminiscent of the promulgations of other planners of the recent past. The desire to decide what is good for others goes hand in hand with progressive limitation of individual freedom and progressive increase in the power of the State.

The idea impresses me as a bit grandiose in its ambition. There is no way of achieving Utopia in one easy lesson.

The value of an idea, if it has value, becomes more apparent upon free and general discussion. The medical profession, I am sure, has no objection to and would favor presentation of such a program to the people, the profession and the hospitals. It likewise would not object to the educational effort to convince these groups of the desirability of parts of the plan. But the presentation must be fair and frank and the right of the medical profession to decide all aspects of the plan dealing with medical care must be respected.

The medical profession recognizes the need for reasonable regulations, licensure and inspection of hospitals, but it would resist perversion of this function of government to bring about an integrated plan of regional organization of hospitals.

It likewise will object to and oppose direct governmental action by legislation and indirect efforts to accomplish this end by selective use of tax funds.

Evolution of ideas is superior to revolution. Compulsion is anathema to the American people and the medical profession. The main objectives of regional organization may be brought about in time if their wisdom and desirability can be demonstrated, but this can be accomplished only on a voluntary basis.

Let us proceed in this manner with due regard for all the elements of medical care involved and on a basis of mutual respect and cooperation. Only in this way can we hope to achieve constructive results of importance and permanence.



## X-Ray Diagnosis and Therapy in Arthritis

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**S**ATISFACTORY diagnosis of the arthritides is frequently difficult except by roentgenographic study of skeletal structures. The late S. Gilbert Scott of London in his monograph on the roentgenological examination of the hands in the arthritides dubbed the hand "the calling card of the arthritic patient." In his book he stated that in systemic forms of arthritis the hand is usually involved even though there may be no subjective findings locally.

Four main types of arthritic or rheumatic conditions are seen by physicians with much greater frequency than are other types. They are the following:

1. Osteo-arthritis (synonyms: Degenerative arthritis, hypertrophic arthritis). This form of arthritis affects both males and females, principally in the latter half of life, and in all climes.

In the hands the distal joints of the fingers appear nodular (Heberden's nodes), and sometimes the distal phalanx is tipped slightly to one side. The roentgenogram reveals narrowing of the cartilages of the joints involved. The involvement is usually bilateral. There may be associated similar involvement of the proximal interphalangeal joints. The articular ends of the bones become broadened and show a tendency toward proliferative bony changes at the periphery of the articular surfaces. The involved joints in the more advanced stages may also show a hill and valley grooving of the badly worn articular ends of the bones. The other joints of the hand and wrist are rarely involved. A very important feature is the normal bone density present. No osteoporosis is present in osteo-arthritis. This type of arthritis is degenerative and is the type also found associated with occupational traumata.

2. Rheumatoid (also called proliferative or atrophic) arthritis is quite a different problem, not only clinically but also roentgenographically. It is found more frequently in women of child bearing age and in emotionally unstable people. It is sometimes found in males. It is not a degenerative disease but is an acute or subacute illness which may be devastating to a few or many of the joints of the body. It is usually found in the joints of the extremities, but it may involve the spine and/or the shoulder and hip girdles.

In the hands there is destruction of the cartilages of the proximal joints of the fingers, the metacarpophalangeal joints, and the carpal regions, and there is fusiform soft tissue swelling about the proximal joints of the fingers. The distal joints of the fingers are uninvolved. It is usually bilateral and in more advanced cases there is frequently ulnar deviation of the fingers. There is a definite tendency, sometimes quite marked, toward osteoporosis. No new bone is laid down about the joints but there is usually

considerable soft tissue proliferation or swelling about the involved joints, hence the term proliferative arthritis. The hands usually feel cold and clammy. When rheumatoid arthritis involves the spine, the joints of the extremities usually escape, and, conversely, when it involves the extremities, the spine usually escapes. The cause of this geographic variation is not understood.

In some cases the first evidence of disease in the back is found in the sacro-iliac joints. When this occurs the first roentgenographic evidence of disease is a loss of sharp definition of the outlines of a part of or all the articular surfaces of one or both of the sacro-iliac joints. As the condition progresses more and more of the definition of the joint is lost until finally the entire articulation takes on a blurred appearance. Later, in rheumatoid arthritis, actual bony ankylosis occurs. Clinically the patients usually have tenderness over the sacro-iliac joints. The degree of tenderness varies widely. Recurrent attacks of low back pain are usual phenomena. (Rheumatoid spondylitis will be discussed later in this paper.)

3. Gout. Only 32 per cent of persons with gouty arthritis show bone changes in the roentgenogram, even in the late stages of the disease. When signs are present on roentgenograms, there are definite punched-out appearing areas in the subchondral bone at the heads or bases of the long bones of the hands or feet. This may be so advanced as to cause destruction of the articular surfaces of one or many joints. Gouty arthritis may be either unilateral or bilateral. In 70 per cent of cases the first attack appears in the metatarsophalangeal articulation of the great toe, and it may appear in this region and not in any other location.

Gout does not always show bilateral distribution in the roentgenograms. However, many cases of gout are not associated with roentgenographic evidence of the disease until late. Gout is much more frequent in males but may be found in either sex after adulthood. It is more frequently found after middle age. It is more destructive when found in young people. The uric acid content of the blood is elevated in about 75 per cent of cases. The disease is sometimes found in people who drink no alcoholic beverages and who live on a simple diet.

4. Non-articular or soft tissue rheumatism causes no bony changes other than occasional inflammatory roughening of the periosteum of the long bones. It is frequently associated with capsulitis and pericapsulitis, as well as inflammation of the sheaths of the tendons. There is evidence of inflammation of the fibrous tissue in the muscles, as was observed by F. F. Roynd. This is frequently fleeting in character and tends toward spontaneous remission in its earlier phases. Later it may be constant and, when chronic, is usually associated with arthritic changes in the joints. It may be as painful as any of the arthritides.

Read before a joint meeting of the Sections on General Practice, General Medicine and Urology at the 76th Annual Session of the California Medical Association in Los Angeles, April 30-May 3, 1947.





## RADIATION THERAPY

Roentgen ray therapy locally over inflamed joints may be used to relieve pain. In this capacity it may be used in osteoarthritis, rheumatoid arthritis, gouty arthritis, or in cases of capsulitis, pericapsulitis, bursitis, or tendinitis. It is quite dramatic in the relief of the intense pain sometimes associated with capsular or pericapsular inflammation, usually three or four treatments sufficing to relieve the pain and reduce the immobility of the joint. In sciatic neuritis, the results of roentgen ray therapy are only partially satisfactory, particularly in acute cases.

All forms of heat treatment make the skin more sensitive to roentgen rays. Hence it is well to avoid such treatment for at least a week before and a week after roentgen radiation has been given. This includes diathermy, hot air, light, short-wave therapy, ointment dressings, plasters, hot packs, etc. Luetics, even when in a symptomless stage, tend toward a stronger skin reaction than other patients.

In advanced osteoarthritic changes in the lumbar region, considerable relief frequently follows radiation of the lumbar muscles. This has been well attested by Kahlmeter in 1929 and again in 1937, by Von Pennewitz in 1933, and Scott in 1937, and by other writers. This is probably due to improvement in the circulation of these muscles and their aponeuroses; with radiation the muscle spasm is lessened. According to Scott, Kaplan, and others, roentgen rays improve circulation as well as increase lymphocytic activity.

Radiation therapy is also of some palliative value in advanced degenerative arthritis of the hip, the so-called *malum coxae senilis*. The relief appears to be largely due to relief of muscle spasm. Radiation therapy does not deter the degeneration of the joint.

The author's radiation technique is briefly, as follows: For the elbow, wrist, ankle, shoulder, hip, and knee, 100 to 150 r per treatment, the dose depending upon the size of the joint, treating twice weekly and employing, over the larger joints, two ports, an anterior and posterior, until four to eight treatments have been given. A second course of four treatments may be given after a rest period of from six to twelve weeks.

Spondylitis of the rheumatoid type, according to the late S. Gilbert Scott, usually begins as arthritis of the sacro-iliac joints; he described cases in which the first roentgenographic evidence of disease was in the sacro-iliac joints. In most of his cases he was able to elicit histories of growing pains through childhood and early adulthood. Furthermore, a considerable number of his patients had been athletes; quite a number of them had been excellent swimmers.

At least 90 per cent of ankylosing spondylitis occurs in men. According to Ehrlich the average age of onset is 31 years. It is not familial.

The disease usually begins with pains or aching in the lower back; frequently the first discomfort is a "lumbago-like" painful attack which comes and goes. Each occurrence is more painful and persistent than preceding ones. The soreness then extends out into the gluteal regions and up the back. Permanent

stiffness, according to Crowe, usually occurs in from one to five years after the onset of rheumatoid spondylitis. During this period the patient loses weight, becomes easily fatigued, irritable and introspective.

Goldthwait and his co-workers, in their excellent monograph on body mechanics, describe the physiologic changes resultant from this postural change. The chest is flattened and the posterior mediastinum is practically obliterated so that the diaphragmatic movements are seriously impaired and portal circulation is thereby greatly decreased.

The inflammatory changes in the soft tissues of the back are followed by calcification in the anterior, posterior and lateral ligaments of the spine as well as of the interspinous ligaments. The so-called bamboo spine is thus produced. It is also known as the Marie-Strumpell spine. With the calcification of these structures the mobility of both the spine and thoracic cage is lost and the patient thereafter stands in a kyphotic posture with the shoulders thrust forward, the chest flat and the lumbar curve largely lost. Lung expansion is much impaired. Though the end result is painless the condition does not burn itself out until the patient is a "burned out spondylitic wreck."

As to treatment, Scott and Kahlmeter are outspoken in their favor of roentgen ray therapy. Kahlmeter stated in 1932 that "there are few fields in x-ray therapy in which the results are so reliable and satisfactory as they are in arthritis." This statement has been well borne out by the experience of Freiburg and many others.

Roentgen ray therapy for spondylitis is as follows: Radiation is given along the entire spine, using a port 10 cm. wide and radiating the entire spine by segments, not more than half the spine receiving radiation at one sitting. A dose of 75 r is given to each field twice weekly for three weeks. Following a rest period of two months, four to six treatments are given as a second course. The patient should then be watched for 12 months and if the condition tends to return, a third and shorter series may be given. Not more than 1,000 r should be given any one field. The clinical response is indeed gratifying. The crippling muscle spasm and pain is overcome and mobility of the spine, so far as muscle spasm is concerned, is restored. No other method of therapy for spondylitis offers the patient this degree of early and lasting relief.

Roentgen treatment for bursitis of joints is dramatic in suddenness of relief at times. For instance, in bursitis of the shoulder, in which the pain is sometimes agonizing, much relief may be experienced 12 to 24 hours after the first treatment. Our experience coincides with that of Young in that there is a higher percentage response in acute cases than in those of longer standing. Four treatments given either daily or at two-day intervals usually relieve the spasm and pain. It is well to take a roentgenogram of the joint before therapy is undertaken, to rule out recent or old fracture and primary or metastatic bone diseases. Also, it is well to know if calcification exists in bursae



about the joint. We know, however, that calcareous deposits are frequently present without symptoms.

Our series of patients treated with wide-field body radiation is too small to warrant discussion. Scott,

in his monograph, "Wide Field X-ray Treatment," reports excellent results. Our limited experience thus far has not given similar response.

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## Acute Central (Hypopyon) Ulcers of the Cornea

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CENTRAL corneal ulcers form a group of ulcers distinct etiologically and clinically from marginal corneal ulcers.<sup>6</sup> In contrast to the latter, which typically are secondary to acute and chronic conjunctivitis, central ulcers are primary in the cornea. The seriousness of the typical (pneumococcal) central ulcer, moreover, is in sharp contrast to the typical benignity of the typical (staphylococcal) marginal ulcer. A further point of difference is that the causal organisms of central ulcers can almost invariably be found in scrapings from the ulcer base while scrapings from marginal ulcers are often disappointing.

The following report summarizes the results of an etiologic and therapeutic study of 50 cases of central ulcer observed by the writer since 1932. They do not constitute a consecutive series since only those cases are included for which records of etiologic determinations were retained and in which therapy was personally administered or supervised.

### CLINICAL CHARACTERISTICS

The central ulcers in this series varied in severity from mild, slowly progressing infections, readily amenable to therapy, to the exceptional fulminating infection which, in the matter of a day or two, progressed to destruction of the eye. As will be discussed later in detail, the different etiologic types, although indistinguishable on purely clinical grounds, varied considerably in severity.

The typical central ulcer arose most often near the margin of the cornea and then progressed in a band-like process into and across the pupillary area. Hypopyon was a characteristic feature in all but three of the 50 cases and tended to develop early in the disease. Pain was severe in most cases and photophobia was prominent in all but four cases in which the ulcers occurred in insensitive corneas. Conjunctival reaction was usually mild.

Although the ulcers could be considered primary in comparison with typical marginal ulcers, they were in fact invariably secondary to corneal epithelial

damage of one sort or another, the most common being that resulting from corneal foreign bodies. Other sources of epithelial damage included rupture of corneal bullae in bullous keratitis, fingernail scratches, and lacerations from branches of trees in agricultural workers. The possibility of an occupational relationship was suggested by the fact that 12 of the 35 pneumococcal ulcers were in coal miners and three of the four pyocyanus ulcers were in railroad trainmen.

### ETIOLOGY

No difficulty was encountered in determining cause in any of the 50 cases. Scrapings from the advancing borders of the ulcers invariably showed the causal bacterium in large numbers, and its final identification was always possible on culture. In sharp contrast to the findings in the series of marginal ulcers previously reported by the writer,<sup>6</sup> there were no cases in which either smear or culture findings were negative. All five of the bacteria found could be recognized in scrapings taken directly from the lesions. Thus an immediate presumptive identification of the infecting organism was always possible—a matter of considerable importance in view of modern antibiotic therapy and chemotherapy.

Table 1 outlines the etiologic findings for the series. In each instance identification of the organism was confirmed in culture. As was to have been expected, the pneumococcus was causal many times more frequently than the other agents. Its nearest competitor was the beta hemolytic streptococcus, with *Pseudomonas aeruginosa* (pyocyanus bacillus) next in order and followed by the *Diplobacillus* of Petit and *Klebsiella pneumoniae*.

The only difficulty encountered in the identification of the bacteria in culture was in connection with

TABLE 1.—*Bacteriological Findings in 50 Cases of Central Ulcers of the Cornea*

(Organisms identified in smear and culture)	
<i>Diplococcus pneumoniae</i> .....	35
<i>Streptococcus hemolyticus</i> .....	6
<i>Pseudomonas aeruginosa</i> .....	5
<i>Diplobacillus</i> of Petit .....	3
<i>Klebsiella pneumoniae</i> .....	1
	50

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Read before the Section on Eye, Ear, Nose and Throat at the 76th Annual Session of the California Medical Association in Los Angeles, April 30-May 3, 1947.



the one Friedlander bacillus ulcer. The familiar problem of distinguishing between *Klebsiella pneumoniae* and *Aerobacter aerogenes* necessitated the use of type-specific sera as developed by Julianelle for precipitin tests. The organism from the ulcer was found to fall into Julianelle's type A.

In Gram-stained preparations the two Gram-positive bacteria, *Diplococcus pneumoniae* and *Streptococcus hemolyticus*, were easy to differentiate since the pneumococci were typical morphologically and invariably encapsulated. The three Gram-negative bacteria were also readily differentiable. Typical diplobacillary morphology distinguished the *Diplobacillus* of Petit while the encapsulation of the Friedlander bacillus distinguished it from the unencapsulated *pyocyaneus* bacillus. The capsule of the Friedlander organism, unlike the capsule of the pneumococcus, stained faintly but definitely with the Gram counterstain and was thus in no danger of being confused with the so-called "retraction spaces" sometimes seen in smears which have been heat-fixed.

#### THERAPY

**Pneumococcic ulcers.** The first 21 of the pneumococcic ulcers of this series were seen prior to 1938, before the sulfonamide drugs came into use. The only chemotherapeutic agent then available was optochin and the results obtained with it were not sufficiently striking for it to have replaced the standard method of cauterization with a thermal cautery. Optochin applied in powder form to the ulcers after curettage of the ulcer base failed to arrest progress in the three cases in which it was tried; in all three thermal cauterization was necessary later. The remaining 18 were all treated primarily by thermal cauterization of the advancing border. This method was generally effective in controlling the infection but good visual results were obtained only when the ulcer had started in the periphery and had not yet advanced into the pupillary area. Cauterization in the pupillary area inevitably resulted in a significant drop in vision. There was no loss of the globe in any of the 21 cases.

Shortly before the introduction of the sulfonamide drugs, serotherapy of pneumococcic pneumonia had come into general use as the result of studies which led to the recognition of 32 distinct serological types. The writer undertook preliminary studies which showed that typing by the "Quellung" phenomenon of specific capsular swelling was a practical procedure, but with the introduction of the sulfonamides the intention of trying serotherapy was abandoned.

Since 1938 cauterization has not been employed by the writer in any case of central ulcer. Reliance has been placed entirely upon sulfonamide and antibiotic therapy, supplemented in a few cases with foreign protein therapy. Sulfanilamide, sulfapyridine and sulfadiazine have all been used. In the first few cases they were given orally only but it was soon realized that in central ulcers topical administration of the drug was of more importance than oral administration. Sulfadiazine was employed orally and topically in eight of the twelve sulfonamide-treated cases,

the topical application being in the form of sulfadiazine powder dusted into the ulcer crater after curettage and into the lower fornix every three or four hours. Atropine was of course used to dilate the pupil. In all eight cases this treatment resulted in rapid resolution of the disease with a minimum of cicatrization. Sulfanilamide was used in the first three cases before sulfapyridine and sulfadiazine, which were found to be much more effective, became available. Sulfadiazine is to be preferred to sulfapyridine because of its lesser toxicity.

Only two pneumococcic ulcers in this series were treated with penicillin but the results were eminently satisfactory. The antibiotic was employed intramuscularly in a dosage of 20,000 units every three hours, and topically in the form of instillations every half hour of a solution containing 1000 units per cc., and in the form of iontophoretic applications of the sodium salt twice daily, according to the method outlined by von Sallmann.<sup>7</sup> In both cases rapid resolution with a minimum of cicatrization resulted.

**Streptococcic ulcers.** The six beta hemolytic streptococcic ulcers were all treated with the sulfonamides, one with sulfanilamide and five with sulfadiazine. The first case of streptococcic infection in the series, which occurred in 1938 just after the introduction of sulfanilamide, was in a young woman who had received a corneal scratch in the pupillary area of the left eye. When the patient was first seen there was dense infiltration in the pupillary area which had reduced the vision in the eye to recognition of hand movements. The ulcer crater itself was about 3 mm. in width. Scrapings from the base showed numerous Gram-positive round cocci in diplococcal form and in short chains, and culture revealed pure beta hemolytic streptococci which were found to have an exalted virulence for the rabbit cornea. Treatment with sulfanilamide was started immediately, a dosage of 1 gm. being given every four hours. Improvement was manifest within 24 hours and healing within three days. The resultant scar was nebulous in character, and vision was 20/30 + one month later. The visual result in this case is believed to have been infinitely better than could have been expected if cauterization, either chemical or thermal, had been used instead of the sulfanilamide.

In the five sulfadiazine-treated cases oral therapy was supplemented by topical applications of the drug in the form of powder or 5 per cent ointment. Response was rapid in all five cases and the resultant scars were small.

**Pyocyaneus bacillus ulcers.** Three of the five *pyocyaneus* ulcers were seen prior to the introduction of the sulfonamide drugs. All three were in railroad employees who developed the ulcers after having had corneal foreign bodies removed in the same office. *Pyocyaneus* bacilli growing in fluorescein used for staining the corneas were believed to have been the source of all three infections. In each case the ulcer progressed to loss of the globe in spite of chemical cauterization combined with topical applications of various antiseptics.

Unlike the preceding three patients, who were re-

ferred for treatment only after the ulcers were well advanced, the remaining two were seen when the disease was early in development. Both were treated with sulfadiazine orally and topically (by iontophoresis and powder) and in both cases the response was good. The resultant scars were minimal.

**Diplobacillary ulcers.** Two of the patients with Diplobacillus of Petit ulcers were seen in consultation and were the second and third of a group of three reported by Chamberlain, Elliot, and Givner.<sup>2</sup> As reported by these authors, the treatment in the first of the two cases consisted in the instillation of 1 per cent zinc sulfate solution three times daily, and the instillation of 0.5 per cent zinc sulfate ointment nightly. Under this treatment the ulcer slowly improved, but as the eye was blind and painful from long-standing glaucoma, enucleation was performed. The second ulcer followed multiple corneal foreign bodies and, without treatment, progressed slowly over a period of five days to cover the lower half of the cornea. Local therapy consisted in a linear keratotomy, topical application of zinc sulfate solution and ointment, and one application of the thermophore at 158°F. to the base of the ulcer for one minute. Systemic therapy consisted in sulfanilamide 1.3 gm. four times daily for ten days, followed by sulfapyridine 1 gm. four times daily for one week. Two injections of foreign protein were given, one of 5,000,000 and one of 15,000,000 typhoid bacilli. In spite of treatment the ulcer slowly progressed and eventually enucleation of the eye was necessary.

The third case of diplobacillary ulcer, observed and treated by the writer, followed a foreign body removal but diagnosis was made early and treatment begun immediately. The foreign body was above and temporal to the pupillary area and the ulcer therefore started in the periphery and spread centrally. Sulfadiazine was administered orally and topically, the ulcer having been curetted thoroughly before the dusting in of sulfadiazine powder. Healing was complete in four days and there was no loss of vision.

**Friedlander bacillus ulcer.** The single case of central ulcer due to *Klebsiella pneumoniae* was in an agricultural worker who received a scratch on the cornea. There developed a slowly-progressing central ulcer, without hypopyon, which responded well to atropinization, curettage, and sulfadiazine orally and topically. Topical applications consisted in iontophoresis with the sodium salt once daily for three days, supplemented by instillations of 5 per cent sulfadiazine ointment every three hours. Healing was rapid, but due to the central location of the ulcer the visual result was poor. The amount of cicatrization was less, however, than would have been expected to result from cauterization.

#### DISCUSSION

The great preponderance of pneumococcal ulcers in this series was certainly to have been expected. Also to have been expected was the lack of clear-cut clinical signs differentiating the typical (pneumococcal) central ulcer from the atypical (pyocyanus, streptococcal, diplobacillary, and Friedlander) cen-

tral ulcer. It should be noted, however, that none of the pneumococcal ulcers showed the slow progression of the diplobacillary and Friedlander ulcers and that, conversely, none of the pneumococcal ulcers had the extremely fulminating character of the pyocyanus ulcers. A possible further clinical difference between the pneumococcal ulcer and the pyocyanus ulcer was that the former tended to progress centrally along a rather narrow track while the pyocyanus ulcer spread out very rapidly to cover the entire cornea. It is of interest also to note that the only ulcers in which hypopyon was lacking were the one Friedlander bacillus ulcer and two of the three diplobacillary ulcers.

In contrast to the difficulty of differentiating clinically among the various etiologic types of central ulcer was the ease with which bacteriological differentiation could be made by means of direct microscopic examination of Gram-stained scrapings. The limited number of bacteria causing central ulcers facilitates their identification and cultures are needed only to confirm the presumptive smear diagnosis. The importance of identifying the infecting organism is self-evident in view of the rapid progress being made in therapy with the antibiotics and sulfonamides.

The role of trauma in the causation of the central ulcers of this series would seem to indicate that damage to the epithelium is a prerequisite to the development of all central ulcers. In this connection it is noteworthy that in the writer's experience a pneumococcal ulcer has never been known to develop in connection with pneumococcal conjunctivitis, even in those extremely severe cases in which secondary toxic iritis has developed. In marginal ulceration of the cornea, on the other hand, trauma plays an insignificant part.

The findings in this series emphasize again the role of solution-bottle contamination in the production of pyocyanus ulcers. As a matter of fact, solution-bottle contamination is probably much more common than the frequency of pyocyanus ulcers would indicate. The organism appears to have a particular predilection for solutions of fluorescein and eserine and has been found by the writer in stock bottles of these two solutions in university pharmacies on two occasions. The explanation for the low incidence of pyocyanus ulcers, in spite of the frequent accidental inoculation of the cornea with the organism, may lie in the experiment of McCulloch,<sup>4</sup> who showed that inoculation of the scratched rabbit cornea never resulted in a pyocyanus ulcer unless the lids were kept closed after the inoculation. Infection almost invariably took place, however, when the lids were kept closed under a dressing. Prophylaxis would appear to consist in (1) the avoidance of contaminated solutions, (2) the avoidance of dressings after foreign body removal when possible, and (3) the use of an antiseptic ointment in those cases in which a dressing is unavoidable. It should be emphasized, however, that contaminated solutions are not the only possible sources of pyocyanus ulcers. The organism has been recovered, though extremely rarely, from patients hav-

ing chronic meibomitis, chronic conjunctivitis, and chronic dacryocystitis, and such patients would naturally be potentially liable to pyocyanus ulcer.

The five bacterial agents found in this series are of course not the only causes of central corneal ulcer but they are certainly the most frequent causes. It is of interest that MacNab,<sup>3</sup> one of the early workers on the bacteriology of corneal ulcers, in his monograph published in 1907, lists the only proven causes of atypical hypopyon ulcer as the streptococcus, the pyocyanus bacillus, and Friedlander's bacillus. He suggests that *Bacterium coli* and *Aspergillus fumigatus* can also produce hypopyon ulcer but later work does not appear to have borne him out. The role of the *Diplobacillus* of Petit in hypopyon ulcer has now become well established, however, although the number of reported cases<sup>2,5</sup> is small. Central ulcers have been observed by the writer in association with gonococcal conjunctivitis, trachoma, vernal catarrh, etc., but in none of these diseases are they typically central and they have therefore been excluded from this series.

Therapeutic results in this series have convinced the writer that thermal or chemical cauterization of hypopyon ulcers is an outmoded procedure and that proper systemic and topical use of the sulfonamide drugs should serve to arrest progress in all but very exceptional cases. In contrast to the frequency of sulfonamide-resistant strains in such bacteria as the staphylococcus and gonococcus, the finding of resistant strains of beta hemolytic streptococci and pneumococci has so far been rare. Data on the sulfonamide-resistance of *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, and the *Diplobacillus* of Petit seem not to be available, but an organism related to the *Diplobacillus* of Petit, i.e., the *Diplobacillus* of Morax-Axenfeld, is inhibited by sulfathiazole and sulfadiazine and it seems probable that the sensitivity applies to the whole group.

The local application of the sulfonamides in central ulcers is of great importance in obtaining effective concentration of the drug in an avascular tissue. In dermatology and surgery there appears to be a trend against the use of the sulfonamides topically, due, presumably, to local toxic effects and to the frequent development of allergic sensitivity. The work of Bellows,<sup>1</sup> which indicates that the sulfonamides tend to increase cicatrization in abrasions of the rabbit's cornea, must be considered, but from clinical observation it would seem that the human cornea tolerates the sulfonamides, particularly sulfadiazine, very well. Von Sallmann's study<sup>8</sup> of sulfa-

diazine applied by iontophoresis to the rabbit cornea indicates that the drug is only very slightly toxic.

In the treatment of hypopyon ulcers the writer has had very little experience with penicillin and none as yet with streptomycin, but there is every reason to believe that penicillin will be the preparation of choice in both pneumococcal and streptococcal ulcers, and that streptomycin will be the treatment of choice in pyocyanus and Friedlander bacillus ulcers. It seems likely that streptomycin will also be found to be active against diplobacillary ulcers although no data to that effect are as yet obtainable. It should be pointed out that there is no contra-indication to the simultaneous use of the sulfonamides and penicillin since their mode of action differs.<sup>9</sup>

#### SUMMARY AND CONCLUSIONS

1. A series of 50 acute central (hypopyon) ulcers is reported. A presumptive identification of infecting organisms was made on Gram-stained scrapings from each ulcer and was confirmed in each case by culture. Of the 50 cases, 35 were caused by pneumococci, six by beta hemolytic streptococci, five by pyocyanus bacilli, three by diplobacilli (Petit variety), and one by the Friedlander bacillus.

2. Therapy with oral and topical administration of the sulfonamide drugs, particularly sulfadiazine, was found to be much more successful than older methods of therapy. The value of the antibiotics, particularly penicillin and streptomycin, is discussed.

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#### Correction

Because of a typographical error in the printing of a formula which was part of "What's New in Endocrinology," an article by George W. Thorn, M.D., which appeared in the June, 1948, issue of CALIFORNIA MEDICINE, the corrected version is printed herewith.

##### Potassium Phosphate Solution:

$K_2HPO_4$  2.0 gm. (K=25 m.eq./l)

$KH_2PO_4$  0.4 gm. (P=14mM/l)

Glucose 60.0 gm.

q.s. ad. 1000 cc.  $H_2O$

To be infused slowly over a period of

two hours.



## Benadryl and Pyribenzamine in the Treatment of Diseases of the Skin

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**B**ENADRYL and pyribenzamine are two new synthetic drugs which have the ability to neutralize the effects of histamine or histamine-like (H) substances which most investigators believe to be identical.

Since Dale and Laidlow<sup>5</sup> pointed out the similarity of anaphylactic shock and histamine effects, numerous methods of specific and non-specific means of combating reactions to histamine have been tried without success. Prior to 1932<sup>11</sup> at least 165 methods or drugs, including sodium thiosulfate, barium salts, non-specific serums and proteins, were tried. In more recent years<sup>8</sup> Vitamin C, barbital, Vitamin P (hesperidin) and ethylene disulfate all have been found to be ineffective or of doubtful value.

Desensitization with histamine itself has not resulted in any success in various allergic manifestations.<sup>7</sup>

Best,<sup>2</sup> in 1929, reported that histaminase would neutralize histamine in vitro, but clinical investigations by many workers, including Best himself in 1940,<sup>3</sup> demonstrated the administration of histaminase has no effect upon histamine spontaneously present in the body or upon that given by injection.

Since histamine itself did not stimulate antibodies, Fell<sup>9</sup> conjugated histamine and horse serum with an azo linkage, called histamine-azoprotein (hapamine). The author's own experience and that of others<sup>6</sup> with injections over many months has shown this compound to be ineffective clinically in many allergic dermatoses.

In 1933 Fourneau and Bovet<sup>10</sup> showed that certain phenolic ethers have the property of counteracting the action of histamine in vivo and in vitro.

In this country, two compounds have been used, benadryl and pyribenzamine. Benadryl is beta-dimethylaminoethyl benzohydryl ether hydrochloride. Curtis and Owens<sup>4</sup> showed benadryl to control acute urticaria in 11 out of 18 cases (61 per cent). Shaffer<sup>15</sup> reported that seven of eight patients with urticaria had been benefited. O'Leary and Farber<sup>13</sup> reported nine of 15 cases of acute urticaria had been completely relieved and that 25 of 35 patients with chronic urticaria had been almost completely relieved. Other authors have had similar results: 70 to 90 per cent relief in acute urticaria; 50 to 70 per cent relief in chronic urticaria. Side reactions to benadryl are quite common. Sleepiness, dizziness and lassitude occurred in 50 per cent or more of patients, oc-

asionally necessitating the cessation of the drug. Other side effects include dryness of the mouth, nausea and excitement.<sup>17</sup> Slater<sup>16</sup> reported an asthmatic patient, taking benadryl, who became so drowsy that he wrecked an electric platform cargo truck.

Pyribenzamine was first prepared by Mayer, Huttner and Scholz.<sup>12</sup> Pyribenzamine is N'Pyridil-N'Benzyl-N Dimethylethylenediamine. They carried out experimental studies and found the drug to neutralize the effects of histamine, both in vivo and in vitro. Arbesman<sup>1</sup> showed relief of 93 per cent of patients with acute urticaria and relief of 75 per cent of those with chronic urticaria. Feinberg<sup>8</sup> found symptomatic relief in pruritus of acute and chronic atopic dermatitis in 16 of 18 patients. Osborne<sup>14</sup> found 23 of 24 cases of acute urticaria relieved by pyribenzamine and the same percentage by benadryl. Urticaria recurred in six of nine patients cleared with pyribenzamine when the drug was discontinued. In atopic dermatitis, the drug was found to be palliative in two-thirds of the patients. Four patients with dermatitis venenata were given pyribenzamine and three responded favorably.

Side reactions to pyribenzamine are less frequent than to benadryl. Drowsiness and lassitude occur in 18 per cent; dizziness in 13 per cent; nervousness and insomnia in 10 per cent; dryness of the mucous membranes in 8 per cent and palpitation in 5 per cent. Most of the reactions are mild and do not necessitate the discontinuance of the drug.<sup>8</sup>

### CLINICAL STUDIES

In this paper we wish to present the studies of the results of the use of pyribenzamine and benadryl in various skin disorders at the Dermatology Clinic of the University of California Hospital, Southern Pacific General Hospital and in private practice. We used the drugs in a total of 241 cases.

Each drug was always given orally, the dose of pyribenzamine in adults usually was 50 mg. four times a day, and that of benadryl 50 mg. three times a day. In some patients it was necessary to reduce this dose 50 per cent. Occasionally it was necessary to increase the dose of either drug to 100 mg. four times a day. In children the dose was computed according to weight; usually 2 mg. per pound. Benadryl has the advantage in children in that the elixir containing 10 mg. per teaspoonful can be used. Pyribenzamine cannot be used in an elixir because of the marked anesthetic effect on the oral mucus membranes and the tongue.

**Penicillin Reactions.** (Urticaria, erythema multiforme). Nineteen cases were followed satisfactorily.

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Read before the section on Dermatology and Syphilology at the 76th Annual Session of the California Medical Association, April 30-May 3, 1947, Los Angeles.



Eight of the patients were given pyribenzamine, and in seven the urticaria cleared in two to three days. One patient was not helped. Nine were given benadryl; in seven the urticaria cleared in two to three days, and one patient was not helped. Two patients were given benadryl and pyribenzamine simultaneously without response over a ten-day period.

*Atopic Dermatitis.* Thirty-seven patients with atopic dermatitis were treated with pyribenzamine or benadryl. Twenty were treated with pyribenzamine over a period of two to six weeks. Three were free of symptoms in one month; 14 were improved and the pruritus was controlled over two to three months; two were not helped. Twelve patients were treated with benadryl with adequate follow-up; four of them were rid of the disease in one month, six were improved and the pruritus controlled in four to six weeks, and two were not helped over a period of six weeks. Five patients were given pyribenzamine and benadryl together; one was improved and four were unaffected. As a rule the drug has to be given over a period of months in order to keep the atopic dermatitis under control. In some patients, taking the drug only at the time of flare keeps the skin clear.

*Pruritus Ani and Vulvae.* Twenty-seven patients were followed adequately. Seventeen were given pyribenzamine; three were relieved within two weeks, ten were better, and all but four were well within one month. Eight patients were given benadryl and five of them were improved within two weeks, while three were not helped. Both benadryl and pyribenzamine were given in two cases without any effect on the pruritus.

*Acute Urticaria and Erythema Multiforme.* Thirty patients with acute urticaria and erythema multiforme were treated with benadryl or pyribenzamine. Pyribenzamine was given in 17 cases; in ten there was relief of pruritus in one to two days and it was cleared within five days; in one case it did not help. In 13 cases benadryl was given; the disease was controlled within one to two days in ten cases, the skin was clear within five days. Two patients had relief of pruritus but it took more than five days to clear. In one case, benadryl was of no help. Two patients were given pyribenzamine and benadryl together without effect.

*Poison Oak Dermatitis.* Twelve cases were adequately followed in this group. In eight the patients received pyribenzamine; in three the skin was clear in one week and the other five there was notable improvement. Benadryl was given in four cases; in one the dermatitis cleared within five days and in two within eight days, while in one it did not help.

*Dermatitis Venenata.* This group contained patients with various types of dermatitis venenata, including reactions to sulfur, sulfonamide and penicillin ointments, soaps, weeds and the like. There are 37 patients in this group. Thirty-three received pyribenzamine. The pruritus was controlled and there was marked improvement within five days in 29 of them. In four there was no help. Benadryl was

given to four patients. Two of them showed definite improvement and relief of pruritus within five days. Two were not helped by benadryl.

*Dermatitis Medicamentosa.* There were 12 such cases. Ten of the patients received pyribenzamine; in four the skin was clear within five days, and four had relief of pruritus and were improved within five days. Two were treated with benadryl. The skin of one was clear within five days; one was not helped.

*Nummular Eczema.* There were 13 cases of this disease. Twelve patients were treated with pyribenzamine. In three the skin was clear within two weeks; in seven the pruritus was controlled and there was definite improvement within two weeks, but in two there was no effect. Benadryl was given to one patient, whose pruritus was relieved in two weeks.

*Post-Scabetic Pruritus.* There were 19 cases. Pyribenzamine was given in 12 cases; six of the patients had clear skins within five days; six were improved and the pruritus well controlled in five days. In seven cases benadryl was given; two were clear within five days; four were improved and the pruritus controlled in five days and one was not affected.

*Stasis Dermatitis With Absorption Phenomena.* There are 17 cases in this group. Twelve patients were given pyribenzamine; in one the condition cleared within a week; seven showed improvement with the pruritus controlled after two weeks, and four were not helped. Benadryl was given to five; in one case the skin was clear within one week; in three there was improvement with the pruritus controlled after a two-week period; one showed no benefit.

*Dermatitis Herpetiformis.* Six patients were treated. Four received pyribenzamine for one month. In one there was improvement with relief of pruritus. Three showed no change whatsoever. Benadryl was given to two patients for a month. One showed improvement with relief of pruritus after one month. One was unaffected after six weeks.

*Seborrhea.* In this group there were seven adequately followed patients. Four were treated with pyribenzamine, all with definite improvement and relief of pruritus. Three were treated with benadryl and improved. Relief of pruritus occurred in two cases. In one there was no effect.

*Miscellaneous Group.* Two patients with generalized pruritus from jaundice were given both benadryl and pyribenzamine separately for one week without any effect on the pruritus. One patient with neurotic excoriations received pyribenzamine and benadryl separately for one month each without change. Two patients with actinic dermatitis showed no benefit from either pyribenzamine or benadryl, each given over a two-week period.

#### SIDE REACTIONS

*Benadryl.* The main side reaction to benadryl is drowsiness and lassitude which occurs in 50 to 60 per cent of patients. Headache occurs in 5 to 10 per cent; nausea in 4 to 5 per cent; excitement in 2 to 3 per cent; urinary frequency, reduction of potency and diplopia in about 1 to 2 per cent. It was ne-

cessary to discontinue benadryl in eight of our patients because of severe side reactions.

**Pyribenzamine.** The main side reaction to pyribenzamine is also drowsiness and lassitude but this is much less severe than that caused by benadryl. These symptoms occurred in 10 to 12 per cent of our patients. The other side reactions such as headache, nausea, excitement, urinary frequency, reduction of potency and diplopia developed in about the same percentage as with benadryl.

#### DISCUSSION

Both pyribenzamine and benadryl have a definite place in dermatological therapeutics. Pyribenzamine has a wider range of use than benadryl because of the lesser side reactions. In some cases, benadryl has a better effect because of the sedative action. Another distinct advantage of pyribenzamine is the antipruritic factor which is much greater than with benadryl.

It should be emphasized that in all cases except those of urticaria, erythema multiforme, penicillin dermatitis and dermatitis medicamentosa, other treatment was carried out simultaneously. This included wet compresses, superficial x-ray therapy, bland shake lotions and the like.

Neither benadryl nor pyribenzamine is a cure for anything. They give only symptomatic relief while the drug is being taken. Urticaria, erythema multiforme, penicillin reactions and dermatitis medicamentosa will all clear in a few weeks with no treatment, but the anti-histamine drugs will relieve the symptoms and shorten the time of reaction. With other types of dermatoses such as pruritus ani and vulvae, dermatitis venenata, poison oak dermatitis and the like, the pruritus is relieved, alleviating scratching and insomnia. This gives local therapy a better chance and the dermatitis resolves in less time.

Since no serious side effects, such as blood dyscrasias, jaundice or death, have been shown to date to be due to either benadryl or pyribenzamine, neither drug should be withheld because of fear of severe complications.

#### CONCLUSIONS

1. Results are presented in 241 cases of various dermatoses treated with pyribenzamine and benadryl.
2. Pyribenzamine is superior to benadryl because of the greater antipruritic element and lesser side reactions.
3. Those dermatoses most helped by benadryl and pyribenzamine include penicillin reactions, pruritus ani and vulvae, urticaria, erythema multiforme, dermatitis venenata including poison oak, dermatitis and dermatitis medicamentosa.
4. The dermatoses helped to a lesser degree include nummular eczema, atopic dermatitis, post-scleretic pruritus and stasis dermatitis with absorption phenomena.
5. In our brief experience dermatitis herpetiformis was not benefited.

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Discussion by JAMES R. DRAKE, M.D., San Francisco

It is admittedly difficult to determine the therapeutic value of new agents such as those under discussion. In general, many workers have continued to use local radiation therapy, dietary exclusions, etc., while at the same time administering benadryl or pyribenzamine. I feel that in practice this is as it should be (outside the realm of pure academic investigation, of course). I would agree that the use of these drugs is palliative and does not relieve the physician of his responsibility for doing an adequate work-up—determining the offending allergens where indicated and taking reasonable measures to eliminate them.

If some of us are disappointed in the results from benadryl and pyribenzamine, it may be because we expected too much. It should be kept in mind that the histamine mechanism is not necessarily the only one in effect in our clinical cases of allergy.

In short, we now have two drugs which if administered with care may give our patients varying degrees of relief. We have, however, no true cure, no panacea, no definite shortcut, no royal road to solution of the allergy problem.

## Standards for the Diagnosis of Activity and Inactivity in the Rheumatic State

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THE difficulties which exist in the diagnosis of rheumatic fever are well recognized and have been discussed frequently in the literature. In recent years, the diagnostic spotlight has shifted from the acute and spectacular forms of the disease in young adults, to the insidious, the latent, and the subclinical forms, especially in children. The latter are of greater over-all importance. Lacking a truly adequate clinical definition of the disease, and lacking a specific diagnostic test, the clinician is frequently beset with perplexing difficulties in establishing or ruling out the diagnosis, rheumatic fever. The growth in our knowledge of the natural history of the disease has explained, but has not simplified, the problems in diagnosis.

The course of rheumatic fever varies widely, not only from patient to patient, but in the same patient, from time to time. One cycle may appear to end in a few weeks leaving no obvious sequel; another may overwhelm the patient and quickly cause death; still another may be one of a number of recrudescences characterized by arthritis, fever and advancing cardiac damage. The clinical picture most often witnessed includes recurrences of symptoms and signs alternating with periods of apparent quiescence, especially in the earlier age group.<sup>2</sup> Thus, the diagnosis "rheumatic fever" is clinically inadequate unless it takes into account the concept of activity and inactivity. This concept is prerequisite to the best handling of the patient, for its goal is preventing or minimizing cardiac damage through proper therapy while activity is present and through the prevention of recurrence in the inactive stage.

A useful tabulation of criteria for the diagnosis of rheumatic fever is that of Jones,<sup>7</sup> who separated the clinical features into major manifestations (carditis, arthralgia, chorea, nodules, and verified history of previous rheumatic fever), and minor manifestations (fever, abdominal or precordial pain, erythema marginatum, epistaxis, pulmonary changes and abnormal laboratory findings). He suggested that any combination of the major manifestations, or the coexistence of one major and two minor manifestations would yield reasonably good evidence for the diagnosis. The criteria of Jones and of others<sup>5,16</sup> have helped to define the clinical diagnosis. Recent descriptions of variants<sup>14</sup> and of atypical<sup>13</sup> or sub-

clinical features<sup>10,11</sup> have extended the present limits of the clinical picture. It is not our object here to stress again the considerable problems in diagnosis and differential diagnosis except to keep clearly in the foreground the concept of rheumatic fever as a long-continued process which involves any or all of the tissues of the affected patient, and the manifestations of which are variable—some, such as acute arthritis and valvular heart disease, being obvious; others, such as carditis, often being clinically obscure. The rheumatic process eventually becomes quiescent, and in the inactive stage, chronic rheumatic cardiac disease is the only known remaining sign. Determining when rheumatic fever has reached the inactive phase is one of the most difficult problems associated with the disease, and every aspect, including history, physical signs, laboratory, X-ray, and electrocardiographic data must be considered in diagnosing inactivity.

### MATERIAL

The material which forms the basis for this paper is drawn from experiences with patients suffering from rheumatic fever or suspected rheumatic fever seen in the Naval Service (1942-46), in the diagnostic clinics sponsored by the California State Board of Public Health and the Heart Division of the California Tuberculosis and Health Association,<sup>12</sup> in hospital teaching wards and in private practice.

### CLINICAL MANIFESTATIONS OF ACTIVITY

Acute carditis is the most important manifestation of activity. It is not only the most frequent, but the most destructive, and it varies from gross, obvious pancarditis to latent, continuing inflammation which is difficult to detect by the most delicate methods now available. It is recognized by tachycardia, variability in heart sounds, rapid increase in cardiac size and in the evidence of valvular involvement, cardiac insufficiency, and acute pericarditis. Taran has pointed out that these signs are inadequate in detecting the milder degrees of carditis.<sup>17,18</sup> He observed that changes in the cardiac rhythm as a result of relative prolongation of systole as compared with diastole will produce a sensitive auscultatory sign of carditis, a kind of tic-tac rhythm, which is independent of the cardiac rate. This can be determined with the electrocardiograph by measuring electrical systole, the Q-T interval. Taran showed that children who were kept at complete bed rest until all evidence of carditis had disappeared (including prolongation of the Q-T time) were better off, as measured by the incidence

The opinions and views set forth in this article are those of the writer and are not to be considered as reflecting the policies of the Navy Department.

Read before the section on General Medicine and the California Heart Association at the 76th Annual Session of the California Medical Association in Los Angeles, April 30-May 3, 1947.



of recurrences and of cardiac enlargement, than were a similar group who were permitted limited physical activities when all evidences of carditis had disappeared except prolongation of the Q-T interval.

Nodules and erythema marginatum are both so closely identified with active rheumatic fever that either can be taken as synonymous with activity. Incidentally, nodules will be found in some patients only if they are carefully searched for, not only in the usual distributions such as the scalp, elbow, and over other bony prominences, but along tendon sheaths and fascial layers any place in the body which is available to inspection and palpation.

Chorea, also, is practically synonymous with rheumatic fever. It is, however, rare in adults,<sup>5</sup> and the full extent of cardiac sequelae may not be detectable for years.

Pneumonitis, acute bronchitis, and acute pleurisy occurring in a rheumatic patient are highly suggestive, but, if they occur in the absence of other signs, are hardly sufficient evidence to indicate rheumatic activity.

"Unexplained" nose bleeds are common in rheumatic children and uncommon in rheumatic adults. If the epistaxis is severe, and sudden in onset, and especially if it is associated with purpura, it is a strong diagnostic point in favor of activity in a known rheumatic. Renal bleeding will occasionally occur in a rheumatic child who also suffers from nose bleeds, and in the absence of glomerular nephritis, cardiac failure or renal infarction.

Migratory polyarthritis, probably because of its obvious and dramatic nature, has been considered the classical clinical manifestation of the disease, and when it occurs in a known rheumatic person can be taken as presumptive evidence of activity. It is relatively more common in the adolescent and young adult groups than in childhood;<sup>2</sup> it is not a constant feature of the disease, however, at any age. Rheumatic activity cannot be positively diagnosed from arthritis alone; in fact, when polyarthritis is rheumatic, other evidences will also be found. Moreover, persistent arthralgia and muscular pain may extend into the inactive stage of the disease.

Fever in rheumatic patients is ordinarily present during the beginning of a rheumatic cycle when other obvious signs of activity are also present, and it ordinarily disappears, especially if salicylates are administered, long before rheumatic activity has subsided. Low-grade fever, especially in apparently healthy children, and particularly if it occurs after exercise, is not to be taken as an indication of illness when it is an isolated finding.

Loss of weight or failure to gain is rather common at the onset of rheumatic fever or at the beginning of a cycle of activity, but a restoration of the body weight to normal is not necessarily indicative of inactivity for, like temperature, a return to normal may precede by long periods the return to the quiescent period.

Acute abdominal pain is not uncommon in rheumatic children, and not very rare in rheumatic adults. It is frequently difficult to decide whether it arises

from acute serous peritonitis, from hepatic enlargement, from acute perisplenitis or acute pericarditis, from pleurisy or from some non-rheumatic source; for example, acute appendicitis. Other evidence is required before abdominal pain can be interpreted as a sign of rheumatic activity.

The pulse rate is considered to be characteristically elevated in acute rheumatic fever, and the elevation is disproportionately high as compared with temperature. Like fever, the pulse may return to normal while activity is still present; however, in such instances, the increment in rate with exercise or emotion may be unusually great or more sustained than in normal persons or in quiescent rheumatics. Slow pulse rates are found during rheumatic activity with second and third degree heart block and with A-V nodal rhythm. In young adults at least, sinus bradycardia and exaggerated sinus arrhythmia are occasionally observed with acute carditis.

#### LABORATORY MANIFESTATIONS OF ACTIVITY

The sedimentation rate is characteristically elevated in acute phases of rheumatic fever<sup>3,14</sup> and constitutes a useful laboratory test for activity. In no sense, however, should it be considered as a specific diagnostic test. It has the following disadvantages as a guide to the presence of activity: (1) It may be altered by salicylates, cardiac failure, anemia, or by concomitant but independent infections; (2) It may return to normal while rheumatic activity is still present;<sup>18</sup> (3) It may continue to be elevated after activity has ceased.<sup>18</sup>

Secondary anemia is a common finding in the acute rheumatism of children<sup>6</sup> but not in adults,<sup>14</sup> especially when milder forms of the disease are considered.<sup>5</sup>

Leukocytosis is an untrustworthy sign of rheumatic activity since it is usually of relatively short duration and may be absent entirely during the most acute periods.

Reduction of the vital capacity is a useful sign of rheumatic carditis which it measures indirectly through the measurement of left ventricular failure.<sup>19</sup> It is a sensitive test, but has the disadvantages of being unsatisfactory for use in small children and in patients with valvular heart disease and cardiac enlargement whose readings, even in the absence of activity, would be reduced.

#### X-RAY CRITERIA

The sudden development of enlargement of all or part of the heart with acute carditis can be observed by x-ray. Occasionally, localized or diffuse dilatation of the aorta or pulmonary artery will be seen during rheumatic fever and will constitute positive evidence of activity in a case which might otherwise be doubtful.

#### ELECTROCARDIOGRAPHIC CRITERIA

Although the electrocardiogram does not constitute a specific means of diagnosing rheumatic carditis, varying degrees of A-V block are classical and are sufficiently characteristic to be of great diagnostic value. Alterations in the contour of any of the in-



dividual waves (P,<sup>13</sup> QRS and T<sup>15</sup>) and in the S-T segments<sup>9</sup> are not rare. When precordial leads are taken<sup>1,8</sup> the frequency of abnormal findings is increased. Ectopic beats, A-V nodal rhythm, shifting pacemaker, exaggerated sinus arrhythmia, paroxysmal auricular tachycardia, auricular fibrillation and the characteristic electrocardiographic pattern of pericarditis may be found.<sup>4</sup> Generally speaking, there will be a direct proportion between the number of films recorded and the number of abnormalities observed. Serial records may be significant, as in myocardial infarction, merely by showing changes from one record to the next. At the same time, the clinician should be prepared to find an occasional case in which electrocardiographic abnormalities have become permanently fixed, although the rheumatic fever has become inactive.

Taran has made careful measurements of the duration of electrical systole in rheumatic children and concluded that it is prolonged significantly in all cases of rheumatic carditis.<sup>17</sup> The prolongation found by him was a function of the severity of the carditis and not of the cardiac rate. From limited personal experience with this criterion of activity, we believe it to be valuable in the diagnosis of active carditis in children.

The various manifestations of activity are shown in order of their probable significance in Table 1.

TABLE 1.—*Clinical Manifestations of Activity in Rheumatic Patients, Other Causes Excluded, Grouped in Order of Significance*

Activity Positive	Activity Probable	Activity Suspected
Carditis (including electrocardiographic evidence)	Arthralgia and Myalgia	Fever
Nodules	Pneumonitis, Acute Bronchitis, Acute Pleurisy	Weight loss
Erythema Marginatum	Increased Sedimentation Rate	Abdominal and Chest Pain
Chorea	Reduced Vital Capacity	Rapid Pulse
Polyarthritides		Anemia
		Leukocytosis

#### RELATIVE INCIDENCE OF ACTIVE AND INACTIVE CASES

The frequency with which active and inactive cases are found amongst rheumatic persons will vary with many factors. Activity will be found more frequently in the younger age groups, particularly children, for then the disease is most active and severe, and recurrences are more common than they are after puberty.<sup>2,20</sup> Active infection will be found most often in those who have had known rheumatic activity in the recent past. The risk of recurrence for the year immediately following an attack, according to Wilson, is 38.7 per cent as compared with 11.2 per cent in the year immediately following one year of freedom from a recurrence.

Activity will be found in proportion to the care with which it is sought, and cannot be definitely excluded in a rheumatic-susceptible unless all criteria for its presence are applied and found negative.

TABLE 2.—*Diagnosis Summary for Seven Hundred Children Receiving Care Through the Rheumatic Fever Demonstration Program*  
Selected Areas in California,\* 1940-46

Etiology	Number	Percent
TOTAL	700	100.0
Active rheumatic	110	15.7
Inactive rheumatic	289	41.3
Congenital (without R.F.)	44	6.3
Non-rheumatic	102	14.6
Unknown	155	22.1

\*The demonstration program was carried out in Solano and Contra Costa counties, with a few children admitted from nearby areas.

During the years 1940-46, facilities for the diagnosis of rheumatic fever were made available in a special clinic for the children of Solano and Contra Costa counties. Of the first 700 children who were referred, 155 were not considered to have received enough study for a final diagnosis and 545 were considered to have been investigated adequately. Of the 545, 399 were diagnosed as having rheumatic fever or rheumatic heart disease, and, of the rheumatic group, 110 were considered active and 289 inactive. Congenital cardiac disease was diagnosed in 44. This is shown in Table 2. Thus, with reasonable, although not necessarily exhaustive examinations (including medical history, physical examination, cardiac fluoroscopy, electrocardiogram, sedimentation rate and blood count), 399, or 73 per cent, of 545 children referred to a cardiac diagnostic clinic were found to be rheumatic, and 27.5 per cent of the rheumatics were in the active stage. The importance of detecting the presence of activity in these 110 rheumatic children is obvious, since for all of them treatment was recommended, and for many of them provision was made for carrying it out.

#### SUMMARY AND CONCLUSIONS

1. The diagnosis rheumatic fever is inadequate for clinical purposes unless it carries with it the concept of activity and inactivity.

2. Various manifestations of rheumatic activity and the difficulties in their interpretations are reviewed, and suggestions for their clinical applications are summarized.

3. The relative incidence of rheumatic fever and heart disease, resolved as to activity and inactivity, in an ambulatory group of 700 California children who were referred to a public diagnostic clinic is reported.

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## Treatment of Superficial Fungus Infections in Routine Dermatologic Practice

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PECK and associates<sup>10,11</sup> first reported the effectiveness of sodium propionate and of a mixture of fatty acids in dermatophytosis. Fatty acids were first used by the baking and dairy industries as inhibitors of molds. Keeney and his coworkers<sup>2,3,4,5</sup> have recorded excellent clinical results with the soaps of propionic, undecylenic and caprylic acids and have concluded that caprylic is the most effective. From the clinical point of view, however, there appears to be no outstanding superiority of one of these agents over the others. Various authors<sup>8,13,14,15</sup> have published favorable reports on undecylenic acid compounds. One study in particular<sup>16</sup> indicated that undecylenic acid and its zinc salt are especially effective in prophylaxis of foot infections. Our experience with fatty acids has been confined almost entirely to the use of 5 per cent undecylenic acid and 20 per cent zinc undecylenate in a special ointment base ("Desenex" ointment—Wallace and Tierman Products Incorporated, Belleville, New Jersey). Another preparation which we have used only in

treatment of tinea capitis is 5 per cent salicylanilide in Carbowax ("Salinidol"—Doak Company, Cleveland, Ohio). Our interest in this compound was aroused by the favorable report of Schwartz et al.,<sup>12</sup> who used it in controlling an epidemic *Microsporum audouini* infection of the scalp.

### DERMATOPHYTOSIS OF THE FEET

The need for an effective agent which could be dispensed without special precautions led to an extensive study during the war at Fort Benning, Georgia. Hopkins et al.<sup>1</sup> found a high percentage of clinical cures among patients treated over four weeks with preparations of undecylenic acid and its salts. The effect was often slow. In the first two weeks of treatment the percentage clinically clear and the percentage relieved of itching was no higher than the percentages achieved with other agents. However, the incidence of irritation was lower than in any other large series. Several powders were tried and found to be relatively ineffective but other authors have reported favorably on the use of more highly concentrated undecylenic acid powder. Solutions in water,

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alcohol and propylene glycol proved more rapidly effective in some patients but were not well tolerated in fissured and denuded lesions.

Keeney<sup>6</sup> felt that fatty acids preparations have a distinct advantage in that they are antiseptic as well as fungistatic. He believed that an ointment containing propionic acid and sodium propionate was as effective clinically as the undecylenic acid ointment for involvement of the feet, the groin and the smooth skin and that either preparation is an improvement over any agent previously employed. It was his opinion that in this respect the treatment of dermatophytosis has been standardized.

Fatty acids higher in the series than undecylenic have been tried clinically on a small scale but no conclusive results are yet available. Hopkins' group also tested several familiar fungicides, including salicylic acid in combination with sulphur, benzoic acid, tincture of merthiolate, and iodine. They stressed the likelihood of disabling dermatitis from their use. However, the concentration of the active ingredients was greater than in the fungicides customarily employed by us. For example, salicylic acid concentrations varied from 3 per cent to 12 per cent, whereas we do not exceed 1 to 2 per cent except for hyperkeratotic involvement. Similarly, sulphur was used in a 10 per cent concentration in ointment form, whereas we prefer to use concentrations no greater than 3 to 4 per cent.

Analysis of 110 cases of dermatophytosis of the feet indicated some general trends, although this series is too small for comparison with such large scale studies as that of Hopkins' group. Practically all our patients were given superficial fractional doses of roentgen therapy because they had relatively severe or resistant types. Forty-seven were treated with a starch lotion containing 5 per cent liquor carbonis detergens. Of those patients, 85 per cent obtained symptomatic relief within two weeks, and 21 per cent were clinically well within a month. Thirty-five patients were given 5 per cent undecylenic acid and 20 per cent zinc undecylenate in a water miscible base, with 77 per cent symptomatically relieved in two weeks and 40 per cent clinically cured within a month. There were two cases of irritation in this group. Thirty-three were treated with 40 per cent alcohol containing approximately 2 per cent salicylic acid and 4 per cent benzoic acid, with 82 per cent symptomatically relieved within two weeks and 36 per cent clinically well. Three had irritations.

Other agents used included 0.5 per cent aluminum acetate solution, 2 per cent crude coal tar paste, potassium permanganate solution, etc. Sixty-nine persons were treated with one of these agents, of whom 87 per cent obtained symptomatic relief within two weeks, and 30 per cent were clinically well within a month. Two in this group had unfavorable reactions.

In this small group of relatively resistant cases the undecylenate-undecylenic acid preparation, as a representative of the fatty acid series, had no advantage in providing rapid symptomatic relief, but did produce clinical cures in a slightly larger proportion

than other agents. However, it was not spectacularly superior to other compounds when used for a period of a month or less. Hopkins<sup>1</sup> emphasized that although the percentage of satisfactory results was higher and irritations were lower than with other agents, these differences were not great. He also pointed out that the advantage of fatty acid preparations became more evident only after a month's treatment. In a group of 509 cases treated with undecylenic acid preparations and followed for less than a month, there were only 43 per cent clinical cures, whereas there were 70 per cent clinical cures in 292 cases observed over four weeks.

Quite often the role of the fungus infection is relatively unimportant, and treatment must be directed toward eczematization, hyperkeratosis, superimposed dermatitis or secondary infection. Fatty acid preparations do not seem to have any advantage in the treatment of the occasional extremely resistant case.

#### DERMATOPHYTOSIS OF THE BODY AND GROIN

Hopkins et al.<sup>1</sup> found that undecylenic acid preparations frequently caused discomfort when applied to the inguinal fold and to the smooth skin. We have seen occasional irritations from their use in these areas. We have had little or no experience with propionic acid preparations, but they are said to be well tolerated. In our limited experience the undecylenic acid ointment was not as satisfactory as one containing 1 per cent salicylic acid and 3 per cent sulphur in water and Aquaphor (cholesterolized petrolatum—Duke Laboratories).

#### TINEA CAPITIS

The present American pandemic became apparent in 1943. We became aware of its existence in the San Francisco area in early 1944. The San Francisco Department of Public Health recorded 717 cases in 1945. The number dropped to 616 in 1946, and 124 cases were reported in the first three months of 1947. Cultures performed in the mycology laboratory of the University of California Medical School from May, 1944, to May, 1946, disclosed 113 *M. audouini*, 58 *M. lanosum* and three *T. gypseum* infections.

Analysis of 142 cases treated by us indicated the presence of *M. audouini* in 130, and of *M. lanosum* in 12. Boys comprised 103 members of the group, and there were 25 girls. The majority had multiple patches throughout the scalp. When single patches occurred, they were usually on the occiput. Kerion was occasionally seen, and generally preceded an early cure. Irritation was rarely encountered, even though medication was used routinely following roentgen irradiation in epilating doses.

In the group of 130 patients with *M. audouini* infections, 20 were lost from observation. In the remaining 110, 85 per cent were cured by one of several means. The hair was cropped closely and was kept short throughout the treatment period. The ointment was massaged over the entire scalp twice daily, and the area was washed with soap and water prior to examination under the Wood light (filtered

ultraviolet) at intervals of two or three weeks. Absence of fluorescence on two successive occasions under this light was indicative of cure. Manual epilation was used when practical. A Westinghouse Purple-X 250-watt lamp used by some parents was helpful, but this inexpensive substitute for the Wood light was inadequate in detecting faintly fluorescent hairs.

Special interest was taken in attempts to cure *M. audouini* infections by conservative means. Schwartz and coworkers<sup>12</sup> were able to cure 56 per cent, their most effective remedies being 5 per cent salicylanilide in Carbowax 1500 and saturated solution of copper undecylenate in the same base. Livingood and Pillsbury<sup>7</sup> reported cures by topical applications in one-third of cases studied. Less successful results were reported by J. Lowry Miller et al.,<sup>9</sup> using several preparations containing propionic acid and its derivatives, as well as some containing undecylenic acid. They were able to cure only about 10 per cent.

In our group, 22 were treated with the 5 per cent salicylanilide ointment, with 55 per cent cures in an average treatment period of two months. Less successful results were obtained in a group of 52 children treated with the undecylenate-undecylenic acid ointment. Only 19 per cent were cured in an average of four months. The failures with both of these preparations were apparent after an average of two months. The largest percentage was cured with roentgen epilation. Of 79 so treated, 84 per cent were cured, fluorescence being absent under the Wood light in an average of two months following radiation. It must be emphasized that the technique of roentgen epilation be left to those especially trained in its use.

#### SUMMARY AND CONCLUSIONS

1. Fatty acid preparations, of which the undecylenate-undecylenic acid ointment is an example, are useful in the treatment of dermatophytosis.
2. They are relatively free from irritating effects.
3. They possess no clinical advantage over a 1 per cent salicylic acid, 3 per cent sulphur ointment in the treatment of dermatophytosis of the groin and body.
4. The resistant type of epidemic ringworm of the scalp was cured in approximately 55 per cent of cases with the use of 5 per cent salicylanilide in Carbowax 1500 ("Salinidol"). Less successful results were obtained with 5 per cent undecylenic acid and 20 per cent zinc undecylenate in a water miscible base ("Desenex"). In this group approximately 19 per cent were cured. Roentgen epilation accounted for approximately 84 per cent cures in children treated by this method.
5. *M. audouini* infections of the scalp should receive a two months' trial with 5 per cent salicylanilide in Carbowax (or some equally effective preparation) before roentgen epilation is used.

Discussion by J. WALTER WILSON, M.D.

The vast majority of the lay public, an even larger proportion of the medical profession, and perhaps all of those specializing in dermatology most sincerely desire a simple

answer to the simple question, "What is the best treatment for athlete's foot?" It must be crystal clear to all of you that such a panacea can never be made available; its advent is rendered impossible by two tremendous obstacles and a host of lesser ones. Of primary importance is the absolute necessity of determining accurately the degree of acuteness of the disease in the individual patient and of predicting efficiently the ability of that particular skin in that particular area to tolerate medication. Secondly, it is always necessary to keep in mind that no fungicide can kill a fungus with which it does not come into contact and that various mechanical barriers to such contact are always present in all fungous infections to a greater or lesser degree. Additional factors such as the specific causative organism involved, complications in the form of other infection or disease, the degree of added dermatitis present, hypersensitivity to fungous products and individual host resistance must also receive due consideration.

The interaction of so many variable factors renders the services of an astute clinician indispensable in many cases of fungous disease. In all statistical studies the clinical ability of the physician making the study must be taken into consideration, else the tyro will be disappointed when he fails to achieve the same results. Dr. Rees has given us ample evidence that he is an excellent clinician; he has utilized this ability in selecting the treatment for each case and in varying the medication as may have been indicated.

It is to be expected that if an astute clinician obtains a certain percentage of good results with a certain medication, one less well trained will achieve a lesser figure. I agree with Dr. Rees that fatty acid preparations are useful at times in subacute tinea pedis and that they are less likely to produce irritation than other common medicaments. I have not had good success with these materials in the more resistant and chronic forms. I believe that the slight degree of acidity produced by these fatty acids plays a part in their efficiency and permits their being tolerated in the more acute phases of dermatomycoses where other fungicides produce irritation. Perspiration, containing as it does fatty acids, is slightly acid when first produced and then possesses some fungicidal activity. It is likely that bacterial splitting of urea into ammonia in old perspiration overshadows this slight acidity and explains the increased incidence of tinea pedis with the advent of summer weather. A denuded area which is exuding serum is also alkaline. Applying fatty acids to such areas as these is of assistance in restoring the normal slight degree of acidity under which skin functions best. Some fungi have the ability to change the medium in which they grow toward the alkaline side which they prefer. Fatty acids act as buffers to prevent the occurrence of such change.

It is also noteworthy that all potent fungicides in general use are slightly or more strongly acid in reaction. The list includes all derivatives of phenol, iodine and sulfur. This fact represents more than simple coincidence, in my opinion.

In reference to tinea capitis it cannot be overemphasized that the primarily important factor is mechanical. Many fungicides are available which are capable of killing any species of microsporum rapidly and completely on contact. The problem is that of causing adequate penetration of the medicament into a follicle which is tightly plugged with a hair shaft and its mantle of fungus spores. No medicament so far available can adequately perform such penetration while the affected hairs are *in situ* and cure is finally attained either because of the spontaneous epilation which occurs in some patients with any type of infection, or the employment of artificial epilation by means of forceps or x-radiation. The patient is cured because the infected hairs fall out or are mechanically removed, not because of the excellence of the fungicide selected. Any one of a number of fungicides will



then suffice, principally by preventing reinfection in new areas and sterilizing the patulous follicles while the new hair grows. The vehicle called "Intraderm" was designed to penetrate intact follicles containing hairs to the greatest possible degree. Fortified with a selected fungicide (TCAP, trimethyl cetyl pentachlorophenate) it has yielded good results in the hands of its inventors. My experience with this material has been encouraging to date although not as good as previous reports would indicate. Salicyl-anilide is, in my experience, a very good medicament for the treatment of tinea capitis.

*Discussion by A. FLETCHER HALL, M.D.*

Without criticizing Dr. Rees for not performing microscopic and cultural tests in the handling of superficial fungus infection in routine dermatologic practice, I do wish to point out that it is impossible properly to evaluate the comparative results obtained by various methods of treatment without such mycologic studies. Furthermore I do not believe it proper to draw any conclusions regarding the relative efficacy of several methods of treatment when all of the patients have received roentgen therapy in addition to the treatment methods being evaluated.

It is entirely possible that an important percentage of the cases in Dr. Rees' first group (where about 20 per cent cures were obtained following treatment with a Liq. Carbonis Detergens shake mixture—and x-ray) may have been a non-mycotic dyshidrosiform eruption; this is also true of the last group in which healing followed the use of various non-specific methods of local treatment (plus x-ray). If the infection in a large percentage of these two groups were non-mycotic while the infection in a large percentage of the groups treated with fungicides were in fact mycotic, the efficacy of the fungicides then would be shown to be relatively greater. Although I hold no brief for the higher fatty acids, I do not believe that they have been given a proper evaluation in the series just reported.

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## An Evaluation of Infertility Factors

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**D**URING the war our study and treatment of infertile couples was much interfered with. So many people changed residence so often that systematic observation and therapy was almost impossible. Moreover, the greatly increased birth rate tended to focus the attention of the obstetrician-gynecologist more on the problem of coping with this reproductivity than on that of enhancing it. But now that the youth of this country is again free to undertake familial responsibilities, our offices and clinics are increasingly besieged by barren couples. This is, therefore, an opportune time for us to take stock of our knowledge in this field and to re-evaluate our techniques for the study and treatment of infertility.

Experienced workers in the field of infertility have made various classifications of the factors which play an etiologic role. In general they are agreed on five principal groups of such factors. These are listed, not in the order of their importance, but in the order of their consideration here.

1. The Coital Factor
2. The Male Factor
3. The Tubal Factor
4. The Female Endocrine Factor
5. The Cervical (and Vaginal) Factor

For a more extensive classification of these groups—correlated, moreover, with diagnostic and therapeutic procedures—attention is called to the excellent one which forms the basis of the brief paper by Page and Page<sup>6</sup> on "An Outline For The Office Investigation of Sterility."

Each student of infertility accords a certain significance and emphasis to each major group of factors. The various opinions are often widely divergent. Our aim will be to cast a little light on the relative importance of these factors, and to attempt to point out where there has been overemphasis and where there may have been insufficient attention. There is not space for even an adequate discussion of specific diagnostic and therapeutic methods, but certain of them have been selected for mention because of common misconceptions concerning them.

### THE COITAL FACTOR

Let us touch only briefly on this factor. That is not, however, to underestimate its importance. In general, a simple but searching coital history plus a post-coital, Hühner test will give us an adequate knowledge of the role it plays in the infertility of any couple. But we have all had the painful experience of being deceived by an occasional wife who at the outset has given a history of what seemed to be satis-

factory sex adjustment, only to discover on later and deeper probing that male impotence, dyspareunia, infrequent coitus, or unannounced coital techniques played a real part in the couple's infertility.

It is in the relationships of this factor, also, that we have made a beginning in the direction of giving due weight to the psychosomatic factor in infertile couples. What part satisfactory sex adjustment plays, for example, in the physiology of reproductive tract secretions is as yet obscure, but we begin to suspect that we cannot ignore it in carrying out a complete infertility study. The determination of the degree and extent of psychic influence on the reproductive soma represents an almost totally unexplored field of which we are just becoming aware, one which may repay us well for our study of it.

We all know, on the other hand, how frequently pregnancy occurs as a result of the most inept coital techniques. The following factors in our list are certainly much more significant in the problem of infertility.

### THE MALE FACTOR

This factor in childless couple does not even now receive the attention it deserves. This is true in spite of the fact that extensive study by specialized workers has vastly increased our understanding of it. Moreover, there is surprisingly good agreement in the literature on how frequently it is the paramount defect in infertile couples. Almost all studies place its incidence in this respect at between 30 and 40 per cent. The casual physician, called upon to explain infertility, unfortunately is not fully aware of this possibility.

That the *male factor* is widely ignored, was forcibly brought home to many of us during army service as we moved from one station to another in this country, attempting to do a small amount of infertility work on army dependents in addition to other duties. It was heartbreaking to encounter the amazing number of young wives who had undergone fairly extensive sterility studies—even major operative treatment—without a spermanalysis ever having been required of their husbands. It was equally discouraging to find that many of these wives thought that their husbands had had adequate semen analysis—when in reality all that had been done was to glance quickly through a microscope to see if motile spermatozoa were present in the semen.

It is true that our present methods of spermanalysis leave much to be desired. They have been likened to trying to determine the character of a person by looking at him from the top of a tall building as he circulates in a mob of people on the street below. Actually, of course, we can tell a good deal about individuals in a mob by observing the behavior of the mob itself. The same is true of spermatozoa. By correlating the characteristics of the mob of sperma-

<sup>6</sup>Presented before the section on Obstetrics and Gynecology at the 76th Annual Session of the California Medical Association, Los Angeles, May 1, 1947.

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tozoa with actual male fertility we reach an indirect estimate of the fertility of the individual fertilizing sperm. The more carefully we observe the sperm mob—the semen, that is—the more satisfactory the correlation becomes. Authorities now agree that simply determining the presence of motile spermatozoa in semen is not a satisfactory criterion of fertility—so the brief glance down the microscope is no longer enough. A minimum analysis should certainly include:

1. The physical characteristics of the semen: Volume, viscosity, and presence of abnormal contents.
2. A careful sperm count.
3. A properly stained differential count of abnormal forms.
4. An accurate estimate of percent of motile sperms at various intervals of a 24-hour period (at room temperature).

Such a semen analysis may well eliminate a long and fruitless search for infertility factors in the wife and lead instead to simple treatment of the husband with early resultant pregnancy. Certainly there is no need to emphasize this important point for the present reader.

#### FEMALE INFERTILITY FACTORS

We come now to discussion of the etiologic factors present in the female. Table 1 presents a collection from the recent literature of incidence figures for the three important groups of factors. It serves to emphasize the areas of certainty and uncertainty in our present knowledge.

##### THE TUBAL FACTOR

Note that the reports on incidence of the tubal factor in infertile women are rather consistent. It plays the major role in 40 to 50 per cent of cases. Thanks to the intensive work of such men as Rubin and Cary the physiology and pathology of this factor are quite well understood. The techniques for studying and treating tubal dysfunction have been so well presented in recent publications<sup>3,9,11</sup> that discussion of them here is not necessary.

One word of warning however should be said. Too many physicians make a final decision regarding the tubal status after only a single tubal insufflation or hysterosalpingogram. The relative merits of the

TABLE 1  
INCIDENCE OF ETIOLOGIC FACTORS IN FEMALE INFERTILITY

AUTHOR	NUMBER OF CASES	CERVICAL FACTOR, DEEMED ACTUAL PRESENT LESIONS	TUBAL FACTOR	ENDOCRINE FACTOR
MAZER & ISRAEL <sup>8</sup>	695	32%	55%	35%
NICODEMUS & RITMILLER <sup>11</sup>	76	4%	50%	69%
WINSON <sup>26</sup>	257	38%	54%	52%
SIEGLER <sup>21</sup>	410	38%	51%	59%
GUERRERO <sup>2</sup>	438	11%	31%	16%
McLANE <sup>9</sup>	372	23%	15%	14%
SHARMAN <sup>19</sup>	500		38%	
THIS SERIES	50	70%		

TABLE II  
INCIDENCE OF OCCASIONAL ANOVULATION IN INFERTILE FEMALES

AUTHOR	NUMBER OF CASES	METHOD OF DETERMINATION	INCIDENCE OF ANOVULATION
KOTZ & PARKER <sup>6</sup>	47	ENDOMETRIAL BIOPSY	36%
ROCK, BARTLETT, & MATSON <sup>17</sup>	392	ENDOMETRIAL BIOPSY	9%
NOVAK <sup>12</sup>	39	ENDOMETRIAL BIOPSY	49%
JEFFCOATE <sup>3</sup>	63	ENDOMETRIAL BIOPSY	25%
EFFKEMANN <sup>1</sup>	81	ENDOMETRIAL BIOPSY	14%
HALBRECHT <sup>3</sup>	130	BASAL BODY TEMPERATURE	12%
MAZER & ISRAEL <sup>8</sup>	695	BASAL BODY TEMPERATURE	15%
WINSON <sup>26</sup>	257	BASAL BODY TEMPERATURE	35%
McLANE <sup>9</sup>	372	BASAL BODY TEMPERATURE	14%
SHARMAN <sup>19</sup>	500	BASAL BODY TEMPERATURE	6%
ZONDEK <sup>27</sup>	2000	MIXED	11%
COMBINED SERIES	4576	ALL	13.3%

two methods would be too lengthy a topic for discussion here; but it has been well demonstrated by Sharman<sup>9</sup> that a single test with either method is subject to about a 10 per cent error. While this error can only be eliminated by repeated tests it can often be reduced by the use of anesthesia, a sedative, or an antispasmodic when the test is performed.

##### THE FEMALE ENDOCRINE FACTOR

One aspect of the female endocrine factor that has received great attention in recent years is the study of defective oogenesis by the determination of anovulatory menstrual cycles—or, if you will, pseudomenstrual cycles. Many workers have placed great emphasis upon absence of ovulation as an infertility factor, and have devoted endless time to devising methods for the hoped-for stimulation of ovulation. But is this an important factor in female infertility in general?

Morton and Hayden,<sup>4</sup> gave us a good baseline for the consideration of this problem. They showed, by means of endometrial biopsies, that in apparently normal women, having normal menses, under the age of 40, who had had one or more pregnancies, the incidence of one or more anovulatory cycles over a moderate period of time was about 7 per cent. In similar normal women, not taking the question of previous pregnancy into account, they found the incidence of occasional anovulatory cycles to be about 12 per cent.

What is the incidence in infertile women?

Table 2 presents a collection of figures from the literature. These figures represent the findings of various investigators in terms of what they considered to be a significant degree of anovulation. Consequently, too much weight cannot be given to them, because the criteria for a significant degree of anovulation are not the same for different workers. Indeed, it is probable that all menstruating women at one time or another have one or more anovulatory

cycles. At just what point such cycles become frequent enough to be a factor in infertility is difficult to decide, and many of the authors in the literature do not state their criteria for making such a decision. The figures of Table 2, however, represent the decisions of respected workers in this field, and as such should carry a certain weight. As quoted, each figure represents the percentage of infertile women in whom it was felt that anovulatory cycles were frequent enough to play a major role in their infertility.

Note the marked divergence of opinion regarding the incidence of significant anovulation in infertile women. One series runs as high as 50 per cent, another as low as 6 per cent. Whether the difference is due to sampling error or to interpretation of the methods used for determination of ovulation is difficult to say; doubtless both factors play a part. If, as seems likely, the former is the more important factor, we can get a better—though still very rough—idea of the true incidence by properly combining these series, using, that is, each percentage figure applied to the corresponding number of cases.

This gives us a total of 4,576 infertility cases with an overall incidence of anovulation of 13.3 per cent. While this figure is twice that for normal women who have borne children, 7 per cent, it is not significantly higher than that for normal women without regard to pregnancy, 12 per cent.

Yet an inordinate amount of attention is being directed to the treatment of this factor in infertile women. So far we have not been able to devise a proven method for direct, immediate stimulation of ovulation. Perhaps this very frustration entices us into redoubled efforts to solve the problem. But should the quest for such a method overshadow study of the other infertility factors?

There is another aspect of the *female endocrine factor* on which we might well dwell for a moment. In certain infertile women we tend to make a rather doubtful assumption. If other sterility factors have been ruled out and if the woman manifests a mild endocrine dysfunction—pituitary, thyroid or ovarian—we are likely to conclude that the endocrine dysfunction is the *cause* of the infertility. In the case of thyroid dysfunction the evidence for this causal relationship is rather good. In the case of pituitary and ovarian dysfunction the evidence is very tenuous. Where such an endocrine upset can be directly related to the occurrence of frequent anovulatory cycles—and where correction of the upset restores ovulation—we are on safe ground. But where ovulation is not in question, to assume that mild pituitary or ovarian dysfunction means the production of infertile ova is very dubious logic. Our knowledge of the physiology of the human ovum is too incomplete to support such reasoning.

What is more important is that this type of thinking may lead to a preoccupation with endocrine therapy which is out of all proportion to its importance and which may turn our attention away from the search for more likely infertility factors.

Both of the foregoing facts are, I think, implicit in the marked disagreement among various authori-

ties regarding the incidence of the *female endocrine factor* in infertile couples. Table 1 shows this clearly.

Nevertheless, the therapeutic approach to infertility with pituitary extracts, chorionic gonadotropins, and ovarian hormones in various dosages and schedules has been labored to the point of absurdity. In conscientious and knowing hands the use of hormone therapy of this type has progressively decreased. Unfortunately, in the therapy of physicians in general its use has steadily increased. Such hormones are now frequently being given purely empirically. They are being given unjustifiably. They are being given irrationally. In some cases they are being given to the definite detriment of the patient. Even a brief comparison of reports in the literature will demonstrate that the percent of pregnancies obtained by those physicians who employ little hormone therapy other than thyroid extract is just about the same as that obtained by those who overdose their patients with all the newest products of the pharmaceutical manufacturers.

#### THE CERVICAL (AND VAGINAL) FACTOR

Unfortunately, dependence on hormone therapy is often at the expense of attention to the least understood but perhaps most hopeful infertility factor, the *cervical factor*. One is much concerned, for example, when it is realized how many physicians carry out prolonged infertility studies and intensive endocrine therapy without ever performing a post-coital, Hühner Test. Yet it is an indispensable aid in pointing to cervical and vaginal pathological changes of such minor degree as to be difficult of direct observational diagnosis though great enough to be a barrier to sperm migration.

That such minimal pathological changes may play an important infertility role is suggested by Siegler's recent paper.<sup>12</sup> He presented 106 cases of infertility in whom study revealed no specific cause and usual treatment methods failed. When a pre-coital douche of Ringer-glucose solution was prescribed for use at the time of ovulation, 29 of these couples conceived. Twenty-seven per cent success is a laudable figure for any type of infertility treatment, and it is to be hoped that sampling error did not enter into it too greatly, or that previously-used treatment did not pave the way for final success. However, in our own last 50 cases of infertility three patients conceived with no treatment whatever other than the pre-coital use of Ringer-glucose solution. One of these three had been infertile for two years but became pregnant at the first ovulation with which the treatment was used.

Whether such a therapeutic result represents a direct effect on cervical and vaginal secretions or whether it represents a stimulation of slightly-below-par spermatozoa is not yet clear; doubtless both factors are involved. Moreover, we are all familiar with the fact that a small percentage of patients become fertile simply as the result of using a therapeutic douche for a short time—and the question of sperm stimulation does not enter here. In any event, present evidence suggests that the beneficial effect



of such therapy so far as secretions are concerned is exerted principally upon those of the cervix, and that artificial alteration of vaginal secretions is of minor importance. That is our reason for classifying *the vaginal factor* only parenthetically with *the cervical factor*.

It may well be that in our routine pelvic examination of infertile women we overlook mild degrees of cervical or vaginal pathological change—or that we have not yet devised adequate methods for detecting them. With regard to the latter, we should cite the important basic work on the physiology of the cervical mucus carried out by Lamar, Shettles, and Delfs<sup>2</sup> and its recent further development by Pommerenke.<sup>7,13,14</sup> Further investigations of this sort are certain to give us more adequate techniques for the study of *the cervical factor* in infertility.

Table 1 suggests how poorly understood—and perhaps how frequently overlooked—*the cervical factor* is today, for the figures reported for its incidence show great variation. To test this conjecture briefly we reviewed our last 50 cases of infertility with special attention to this factor. They were given a minute scrutiny for any evidence of even a minimal cervical or vaginal lesion. Such evidence was considered to be: visible cervicitis, cervical erosion, purulent or excessive cloudy cervical discharge, evident vaginitis, or the finding of vaginal parasites or fungi. According to these criteria, the incidence of *the cervical factor* in our small series of 50 cases was 70 per cent! As might be expected, other, sometimes more important, infertility factors were present in these patients (Page and Page,<sup>6</sup> studying patients from this area, found the average number of infertility factors per couple to be 2.4). But such a high incidence of cervical and vaginal lesions certainly cannot be by chance. We see nothing like it in the normal, fertile woman.

At the present time, however, even meticulous direct observation of the cervix and vagina probably will not always reveal the presence of *the cervical factor*. The Hühner Test, an immensely valuable diagnostic procedure, should never be omitted. Unfortunately, it has not been sufficiently employed and studied to bring its development to a satisfactory high point of neatness and accuracy. Its present technique is rough and gross. Aspiration or sampling of cervical mucus sometimes presents a problem in its dexterous, uncontaminated accomplishment. Methods for sampling from different levels of the cervical canal are only now in a process of development, and bid fair to provide significant findings. At present the interpretation of Hühner Test findings is not even well standardized—as is attested by disagreement between outstanding workers in the field.<sup>8,15</sup> Selection of the optimum time for the test, that of ovulation, is not rigidly adhered to so that the findings of many users are misleading. While it was originally felt that the test should be carried out within one to two hours after coitus, recent work suggests that more valuable information may be gained at four to six hours.

It is evident that the Hühner Test has not reached its full development. Its wider use, therefore, with refinement of its technique seems imperative; for it promises to give indispensable information about infertility factors. Many possibilities are open to those of us who will give this valuable investigative procedure its proper place in our armamentarium.

Along with our diversion of attention from *the cervical factor* our methods of treatment of cervical lesions have remained almost at a standstill. Indeed, in view of the delicate physiology of the cervix and the nicely balanced cervico-vaginal chemical relationships, one wonders whether some of our more vigorous therapeutic methods may not have left the patient more infertile than she was prior to their use. Too deep a cauterization may produce unfortunate cervical sequelae. Too extensive conization may remove too many of the essential mucus-secreting glands. Too vigorous chemical treatment may produce a chemical inflammatory reaction in the cervix which offers as much of a barrier to ascent of spermatozoa as did the original cervical lesion. We are just beginning to consider the use of our newer antibiotic and chemotherapeutic agents in the treatment of cervical and vaginal infections, and other, more delicate methods are only dimly envisioned. But unless we place proper emphasis on the importance of *the cervical factor* in infertility, the development of these methods will continue to lag.

We have all tended, in our desire to aid the often-pitiful infertile couple, to grasp at straws in our attempts to elucidate the factors involved. The Rh factor is a case in point. Rh incompatibility has been called in question as a possible etiologic factor in infertility. Recent papers<sup>1,5</sup> have already shown rather convincingly that the previously-assumed role of the Rh factor in the causation of early abortion is mythical; it is even less likely that the similar assumption regarding its role in infertility is a valid one.

Rather than devote too much of our time to grasping at such straws let us return to a more searching study of familiar but poorly-understood infertility factors. Of these *the cervical factor* is perhaps the most deserving of our attention.

Discussion by PENDLETON TOMPKINS, M.D., San Francisco

I have been wondering in what respect the specialist in sterility possesses an advantage over the general practitioner. The difference is not in knowledge (for Dr. Overstreet has refreshed our recollection of the factors essential for reproduction), nor in equipment (for the specialist possesses no instruments not found in the office of the general practitioner excepting a curette for office endometrial biopsies and a machine for tubal insufflation). Even these two instruments may be temporarily dispensed with, for the basal temperature graph gives information regarding ovulation which is comparable to that provided by endometrial biopsy, and a uterosalpingogram is a substitute (though a poor substitute, in my opinion) for tubal insufflation. Since the specialist requires no rare knowledge and no indispensable equipment, what is the basis for his reputation? Simply this: thoroughness. He takes the time to secure a complete history, he procures blood counts, urinalyses, Wassermann tests, basal metabolism tests; he secures accurate temperature graphs and

records of coitus, and he insists upon complete sperm counts. Dr. Lewis Michelson of San Francisco, one of the eminent students of male fertility in this country, requires studies of three different specimens of semen before evaluating male fertility. He feels that a single specimen may be exceptionally good or exceptionally poor and quite unrepresentative of the normal of the individual.

The specialist in female infertility will scrutinize the cervix with a more critical eye than any other gynecologist. It does not suffice that there is no gross evidence of endocervicitis. The cervical mucus should be examined for leukocytes indicating cryptic endocervicitis. The canal should be delicately probed to discover pockets, synechiae or adhesions. These are important, not because they obstruct the passage of sperm, which are after all much smaller than a red blood cell, but because these pockets interfere with cervical drainage and are associated with abnormal cervical mucus. In every study the cervix should not only be gently probed and sounded but also should be slightly dilated. I have often wondered what part cervical dilatation has played in those cases of conception which have followed "the initial examination," an endometrial biopsy without other treatment, or a single tubal insufflation. In such cases the passage of an instrument through the canal may have been more beneficial than was recognized.

Endocrine therapy has been used in many forms and according to many schedules to stimulate ovulation or to increase the sperm count. If our present evaluations are correct the only certain effect of such therapy is to delude at least one person—the physician administering it.

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## Surgical Operations Upon the Aged

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THE number of patients in the advanced age group increases with each passing year. We are told that 80 years ago, at the close of the war between the States, the average life expectancy of a baby was 40 years. Today it is 60, with the indications of a still further extension of the life span. There are in our country today approximately 10 million persons of an age of 65 or beyond, and the infant born this year, if he attains his 65th birthday, should find himself one of twenty million as old as he is or older. The care of this group enters the life of every physician, and this discussion pertains to the surgical aspect of that service.

What constitutes the "aged" patient? We have mentioned 65 as a working point, yet certainly age itself is not determined by the calendar. Circulatory

deficiency, renal impairment, obesity, diabetes, and many other conditions may so alter the picture that an individual becomes older than his stated age. For clarity in this presentation it will be assumed that we are speaking of patients past 65 who are normal for age, or of those perhaps younger with unfavorable factors which bring them up to the same life expectancy. The term "surgical age" would be a good one and might well be used in each doctor's record showing his estimate of that patient as compared with an imaginary normal. Thus an individual of 60 might be tabulated as having a surgical age of 70, if in the opinion of his physician his condition was no better than the normal for the latter group. Such a classification might prove valuable in considering the advisability of elective surgical procedures.

The most common conditions contributing to a poorer-than-normal status are, in the order of this writer's prejudice, cardiovascular disease, obesity,

Read before the sections on General Practice and Anesthesiology at the 76th Annual Session of the California Medical Association in Los Angeles, April 30-May 3, 1947.

renal insufficiency, diabetes and a senile or poor mental outlook.

Cardiovascular disease, because of its far-reaching secondary effects, must head any list of unfavorable factors in patients past middle age. Certain phases, such as congestive heart failure, cardiac asthma and emphysema, may create an almost prohibitive surgical risk. On the other hand, arteriosclerosis without symptoms, hypertension and coronary disease are not necessarily deterrents. It is rare to see a patient with a heart known to be poor, or one with damaged coronary arteries, act badly during or following an operation. Forewarned being forearmed, a skilled cardiologist is brought into the picture both pre- and postoperatively. With surgical trauma minimized as much as is humanly possible, the blood pressure carefully maintained at the preoperative level and with early ambulation, these patients do surprisingly well.

Obesity, in the opinion of the writer, is a commonly ignored yet most potent deterrent to a successful surgical result. Larger incisions, lengthened operating time with increased tissue trauma, anesthetic difficulties, poor wound healing, the inability of the patient to move himself postoperatively or to practice deep breathing, and the impracticability of early ambulation add up to a tremendous total in the mortality and morbidity tables. If a surgeon performs one hundred cholecystectomies in older patients with normal physique and 95 will live, and in a parallel group of grossly obese the recovery rate is 90 per cent, it would seem that there is but 5 per cent difference in the two series. But turn the figures around—five deaths in one group against ten in the other—and the mortality rate is seen to be twice as high. A longevity table prepared by Joslin from Bortz compares a group of nine obese individuals age 40 with nine of normal weight. At sixty the survivals are six against eight; at seventy, three against five; and at eighty, one compared to three. Since the cure of this malady can be effected through supervision and self-discipline, it does not seem amiss to suggest that elective operations in the grossly obese be declined or postponed. It is fair neither to the surgeon nor to the patient to assume an unnecessary risk.

Renal insufficiency is so closely linked with cardiovascular disease that it might well have been included in that classification. The occasional acute kidney failure with anuria is, however, so formidable a complication that it deserves special mention. Here prevention is far more valuable than cure. A careful history, combined with a nonprotein nitrogen value, a urea clearance test, a measured 24 hour output, and sometimes catheterization for residual urine, may avoid a fatality. Postoperatively the best guide is the excretion of at least 1000 cc. of urine per day with an acceptable specific gravity. If oral intake does not produce this, intravenous fluids are indicated. Those solutions made up with saline should be limited to 1000 cc. per day. Glucose in water may be used in any amount desired.

Diabetes if neglected can prove acutely dangerous, yet if it is controlled the operation can be made quite

safe. In operating on a diabetic the surgical procedure can never be taken in stride. An internist skilled in the treatment of this disease can bring the patient to the operation timed almost to the minute and in perfect carbohydrate balance, and supervision by the internist should continue through every step of the postoperative period, especially when solutions of glucose are used. There are few occasions in surgery where so close a liaison of professional services is required.

A poor mental outlook is another unfavorable sign. It is very difficult to help a patient through a dangerous situation who has neither a spirit of cooperation nor the will to live. This attitude may be sensed in advance. It may be brought out by friendly conversation on other than medical subjects. Is he alert? Is he interested in current events? Has he a hobby and does he show a genuine interest in living? From such an interview one can form some estimate of the degree of brain cell degeneration. Certain it is that an elderly patient who is alert, cooperative and who really wants and expects to get well, will do far better than one who is depressed, disinterested or resigned—senile.

The advances made in the specialty of anesthesia have probably contributed more toward the safety of the aged surgical patient than has any other one factor. The old are never good anesthetic risks, and there is nothing more gratifying than to observe the skill with which the expert anesthetist handles his responsibility. All anesthetic agents are depressing and these patients should not be depressed. It is this writer's practice to choose only the best anesthetist, to acquaint him with the contemplated procedure and expect that he see the patient the night before operation. The choice of sedatives and anesthetic agents is then left in his hands. This ideal, however, cannot always be attained and where such is the case the usual routine is modified as follows.

All premedication is reduced. If a barbiturate is used the night before, it is limited to one capsule. The morning of operation, if the patient be small, very old or weak, it is again limited to a single capsule and the opiate is reduced to about one-half the usual dose. These drugs are administered far enough in advance so that their full effect is obtained before the anesthetic is begun. Induction of unconsciousness with pentothal or nembutal intravenously has become very popular and justly so, but the anesthetist must be watchful of the temporary respiratory depression, and be prepared to combat it if it persists too long. An airway, a laryngoscope and an oxygen tank are "musts" in the equipment within reach.

So many combinations of anesthesia are now available that it would be cumbersome to attempt to discuss them. Bare unconsciousness with pentothal plus local infiltration may be indicated at times. A preference is admitted for spinal instead of general anesthesia in most cases. By keeping the spinal dose small and again using pentothal sparingly, muscular relaxation is obtained with the patient lightly asleep. For leg amputations a hemispinal is perfectly feasible. In this, with the patient lying on the affected



side, a small amount of a heavy solution is injected. This sinks against the nerve roots on the dependent side and anesthetizes that leg only. Spinal anesthesia seems to present but little hazard to the aged patient provided the dose be small, the level of the anesthesia be kept below the intercostals, and the blood pressure held at the pre-anesthetic level with ephedrine. General anesthesia by inhalation, however, has been our standby for years and meets with no objection from the writer if muscular relaxation can be obtained without carrying it to a deep level. This is often difficult to accomplish.

In operating room preparation all efforts possible should be made to avoid the loss of body heat. Old people feel the cold, and are depressed by it. All skin disinfectants evaporate quickly and chill the surface. An avoidance of overexposure plus warm blankets over the covered parts should be the rule.

As to operative technique, every refinement of gentleness and hemostasis at the surgeon's command should be used on aged patients. Speed is no object if attained through rough handling. The older the patient, the greater the liability to shock, and this is usually brought about by tissue trauma and blood loss. Patients with thickened blood vessels actually have a diminished blood volume so that any loss becomes proportionately greater. No one single item adds so much to the safety factor as does a blood or plasma transfusion running during the operation. This is far more advantageous than its administration before or after. Non-elastic blood vessels do not take kindly to sudden rises and falls of pressure, and shock once developed is hard to combat.

Old tissues heal more slowly than normal. The abdominal closure is therefore subject to two demands, namely, that the wound edges be safely held as long as is necessary, and that the closure be of sufficient strength to allow early ambulation. Silk and cotton meet these qualifications, and cat-gut will also if it is reinforced by many retention sutures of non-absorbable material. An instructive observation came from a study of wound ruptures in the largest hospital in Los Angeles. In every case of disruption retention sutures had been used, but in no case more than three.

The aim of postoperative treatment should be toward prevention of those complications most likely to occur. They are pulmonary, renal, and circulatory. Oxygen, either by tent or mask with frequent CO<sub>2</sub> ventilation is a valuable safeguard against the first and last of these. Saturation of the blood with oxygen aids the heart in its task of increased oxidation. Frequent turning of the patient is advisable but may be overlooked unless specifically ordered. Morphine is just as valuable as it is in younger patients, although the dose should be smaller. Barbiturates are used sparingly if at all, because of their tendency to confuse and depress.

The kidney function in old people is notoriously poor. Intake and output should be charted, and the latter not allowed to fall below 1000 cc. per day; 1500 cc. were better. If output is below 1000 cc. a day intravenous fluids must be increased. Five to ten

percent glucose solution in water seems to work best. Frequent voiding of small amounts calls for catheterization for residual urine. In wasting diseases where hypo-proteinemia can be assumed or proven, amigen is of extreme value. Vitamins, especially C, are used routinely to favor wound healing.

Early ambulation has recently been the subject of much favorable discussion. Whatever its merits may be, they are magnified in the aged. Nothing is more conducive to a return of morale. Bowels and kidneys act more promptly, gaseous distension and catheterization are minimized, appetite returns more quickly and a more hopeful attitude is apparent. From all reports, wound disruption is not increased by early ambulation. This last may be true, but because of the responsibility the surgeon assumes in departing from a conservative precedent, this writer suggests that incisions be sutured with an eye to additional security if early rising is contemplated.

Age itself is no barrier to surgery. The writer is fully aware that this paper offers nothing new. It will have served its purpose if it reminds us afresh that in no other class of patients do careful precautions and attention to detail mean so much. Life is often just as precious to its owner at 70 as it is at 30, and because of his diminished sphere of living pain becomes even more intolerable. Surgical risk is greater—just how much may be hard to determine. We are told that ordinary surgical mortality becomes doubled at 50, trebled at 60 and quadrupled at 70. This affords an opportunity to consider elective operations from a statistical or mathematical angle.

Nothing is more uncertain than one life; nothing surer than the law of averages on a million lives. The tables of life expectancy used by insurance companies are highly accurate when applied to a group. At 50 and normal for age, a man's life expectancy is 20 years or to age 70. For each year that he has lived beyond 50, one-half year is added to 70. Thus at 60 his expectancy would be to 75, at 70 to 80, and at 80 to 85. In the older brackets it may sometimes be well, therefore, to think of life not as an abstract whole, but rather as a definite sum of year units. Surgical measures with their attendant dangers and chances of failure then help form an imaginary equation. If the reward for success (a full life expectancy) is not greater than the surgical risk plus the patient's expectancy under palliation (which is forfeited when operation is performed) then perhaps the more radical course should be abandoned.

No part of this discussion pertains to the necessary emergency operation, no matter what the odds may be. Nor does it apply to operations for those in constant pain. These patients are entitled to any choice they may wish in seeking relief, for although life may be estimated in units of years, living is measured in terms of comfort. Outside of these, however, there will always remain a group of elective conditions in which surgical operation may offer something more or take everything away. It is toward these cases that the mathematical angle may help point the way in estimating expected gain against possible loss.

1930 Wilshire Boulevard.



# The Present Status of Female Sterilization Techniques in the United States

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THIS study was undertaken to discern the methods of sterilization used by leading gynecologists and obstetricians in their own practices. Although there are many carefully prepared and critically analyzed reviews of tubal sterilization techniques presented at regular intervals in the literature, each of these studies is presented to extol the virtues of one technique. To crystalize the opinions from the various sections of the United States, we have sent a questionnaire to the members of the teaching staffs of the medical centers and in this paper we have summarized the returned answers.

Historically, sterilization of the female has been of interest to the medical profession since first contemplated by Hippocrates as a means of eliminating hereditary perpetuation of the insane. It is difficult to trace accurately the earliest attempts at sterilization because we have reports of cesarean sections in Sanskrit translations on ancient Hindu medicine from the fifth century. There are Biblical references to cesarean operations in Jewish history from the second century.<sup>4</sup> It is not illogical to assume some attempts at sterilization were made in the early centuries.

In the early part of the Nineteenth Century, G. P. Michealis suggested hysterectomy with cesarean section for sterilization, and in 1834 von Blundell removed the uteri from four rabbits. Of the four rabbits hysterectomized, three lived, giving reassurance to those who were to attempt gynecological surgery in the years following. His technique included bringing the stump of the cervix to the abdominal wall, a forerunner of Porro's operation, introduced in 1877. Von Blundell is also credited with the initial written suggestion of tubal sterilization in his textbook, published in 1834. The method he suggested was tubal resection, but he wrote that simple division might successfully prevent pregnancy.

Froriep, in 1850, suggested the creation of a chemical slough stricture in the upper uterine angles to prevent pregnancy. This was the forerunner of the recent suggestions for sterilization by intrauterine cauterization. During this era, the uterus was thought to have definite endocrinal function, so hysterectomy was rarely done for primary sterilization. In 1880, Lungren of Toledo, Ohio, tied both tubes after a second cesarean operation; this is the first recorded truly tubal sterilization. It is of interest to observe that that his follow-up notes elaborated upon the regular monthly menstruation after the operation, indicating the paucity of knowledge about the physiology of menstruation at that time.

Between 1880 and 1910, a wide variety of procedures were carried out with uniformly poor results. A report by Leonard<sup>8</sup> in 1913 emphasized the high incidence of failure in all methods of sterilization, including cornual resection, intra-uterine cauterization, and total salpingectomy. Nurnberger's report in 1919 described 36 methods of tubal sterilization and concluded that salpingectomy or cornual resection was the best. The large number of procedures in his report emphasizes the keen interest in perfecting a reliable technique.

Madlener's publication in 1919 received widespread acclamation in this country and in Germany. The certainty of the results, however, were questioned as early as 1921 by J. Whitridge Williams,<sup>13</sup> although in 1926 and again in 1932 Madlener published two series without known failure.

Many new techniques were developed from 1920 to 1940. Unusual among the procedures suggested for sterilization was intra-uterine actual cautery to the tubal openings, propounded as a "simple office procedure,"<sup>11</sup> and the creation of a double vagina, one to be a blind pouch for coitus, and the other for pregnancy.<sup>5</sup>

Von Groff<sup>10</sup> reviewed 4,279 cases of sterilization by the Madlener technique, wherein he made critical analysis of the failures. He attributed them to slipping of the ligature, laceration of the serosa which encouraged fistula formation, and tying of the round ligaments by error. He concluded that the failures resulted from not adhering to Madlener's exact technique.

Dippel<sup>2</sup> in 1940 studied postoperative tubal specimens with serial microscopic sections from five patients who became pregnant after sterilization by Madlener's method. He reemphasized von Groff's findings on the technical failures, and demonstrated two cases of endosalpingiosis, a process which Sampson publicized in 1921.

Lazard,<sup>7</sup> in 1940, reviewed the entire subject and concluded that subtotal hysterectomy was the most satisfactory procedure.

In 1933 and again in 1939, Lull<sup>9</sup> reported extensively upon the method of tubal sterilization introduced by Pomeroy, stating that in his clinic the method had given exceptionally fine results. His careful analysis of the reported failures of the Pomeroy method bears out the importance of exactly adhering to the technique. His papers offer proof that Pomeroy's technique is the simplest and safest of the tubal type sterilizations.

In 1946, Knight<sup>6</sup> compared the results of the Pomeroy operation with the published statistics on the Madlener method. He concluded that the 0.31

Read before the Section on Obstetrics and Gynecology at the 76th Annual Session of the California Medical Association, Los Angeles, April 30, 1947.

per cent failure in the Pomeroy operation was better than the 0.6 per cent average of failures in a large series of the Madlener type.

Any discussion of sterilization procedures cannot circumvent the problem of endocrinal failure attendant to the operation for sterilization, and for that reason a brief review of the literature is presented. Lungren's contribution that tubal ligation did not interfere with menstruation has been mentioned. Dippel,<sup>3</sup> in 1939, demonstrated that only 16.6 per cent of patients had menopausal symptoms following hysterectomy, when sterilization was the primary indication for surgical operation, but that more than 67 per cent of the patients who had a hysterectomy for definite pelvic disease complained later of menopausal symptoms. He concluded that involvement of the ovaries in the disease, rather than the hysterectomy itself, was the principal cause of endocrine failure.

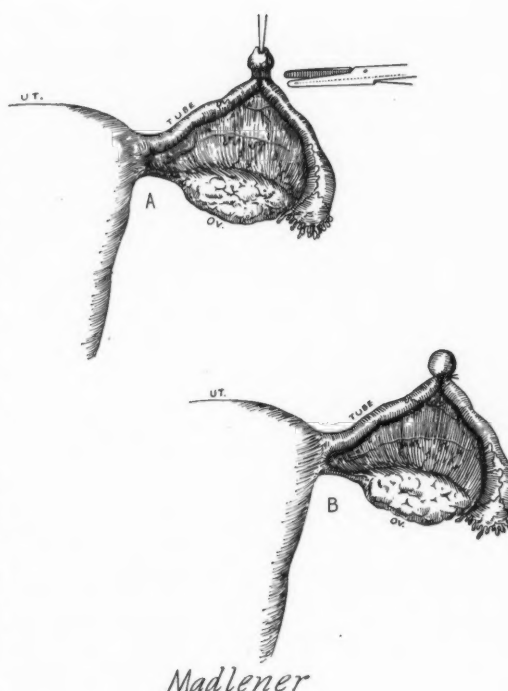
Vruwink<sup>11</sup> and Papenoe undertook an exhaustive study of libido following sterilization in 1930 and concluded that one woman in four does not enjoy coitus after sterilization, but that this fact is not mentioned to the surgeon, usually because he does not ask about it. They also concluded that bilateral salpingectomy did not affect libido; in fact, one third of the patients reported improved sex life when pregnancy was no longer feared. Hysterectomy, plus salpingectomy, had no demonstrable effect on libido, according to their records. It is of interest to discover in their conclusions that bilateral oophorectomy may leave the well adjusted woman with no change in her satisfactory sex life, but that the young, unadjusted and near menopausal woman is usually quite dramatically affected; her libido is markedly decreased. Watson<sup>12</sup> concluded that the removal of the uterus does not tend toward earlier menopause.

After careful perusal of the available history of sterilization which has been presented here in condensed form, it is concluded that the following five methods of tubal sterilization have apparently survived the test of time and are in common use. These were the basis for our questionnaire and the methods seem to serve most obstetricians and gynecologists in the United States. Many indicated that they used variations of several of these methods and only one or two used a new technique.

1. Madlener sterilization which consists of bringing up the fallopian tube through a small abdominal, or posterior colotomy incision, crushing its middle third and tying the loop with non-absorbable suture. (See illustration).

2. The Pomeroy technique (see illustration) which resembles the Madlener operation, in that it can be done through the small abdominal or posterior colotomy incision. The tube is grasped in its mobile middle third and pulled up to a loop, which is tied with fine absorbable catgut. There is no preliminary crushing of the tube. The loop lying above the tie is then excised and after a very careful check for bleeding, the tube is dropped back.

3. The cornual resection (illustrated) which consists of the excising of the cornual portion of the tube in a wedge shape. The margins of the incision are carefully closed and



the bleeding arrested. The remaining cut end of the tube is buried into the broad ligament and the raw areas covered with the round ligament.

4. The method devised by F. C. Irving. He divided the tube in its middle third and buried the cut end of the proximal portion into the myometrium of the posterior corpus. (See illustration).

5. The Watson method of tubal sterilization which consists of excising the middle portion of the tube and burying the proximal cut end into the broad ligament, as shown in accompanying illustration. The distal cut end lies free in the abdomen.

Upon the background of the historical and literary review of the sterilization problem, we present the results of the questionnaire sent to leading members of the American Board of Obstetrics and Gynecology in each section of the country. A distinct effort was made to send queries to men closely affiliated with medical teaching centers. Table 1 is a replica of the questionnaire answered by 124 of these men.

We received replies from more than 70 per cent of the doctors. Many of the remaining questionnaires were returned unanswered because of war displacement.

The returned questionnaires have been analyzed in several ways in an attempt to show: (1) Which procedure for sterilization is the most universally used by obstetricians and gynecologists. (2) What change in procedure is made when sterilization follows cesarean section or is a part of laparotomy; (3)

TABLE 1.—*The Questionnaire Which Supplied the Data for This Study.*

Which of the following methods do you employ as a usual routine in sterilization?

	Following Cesarean	With Laparotomy
a. Pomeroy.....	.....	.....
b. Madlener.....	.....	.....
c. Cornual resection.....	.....	.....
d. Watson.....	.....	.....
e. Subtotal hysterectomy.....	.....	.....
f. Other.....	.....	.....

What percentage of cases do you *estimate* show menopause symptoms one to three years after hysterectomy when that operation has been performed on women under 30 years of age?.....%.

Regional influence from adjacent medical centers upon procedures chosen; (4) The impressions of obstetricians and gynecologists concerning the onset of menopausal symptoms following hysterectomy in women under 30 years of age.

It was difficult to decide what definition could logically be applied to the regions selected. The influence of medical schools and prominent authorities in geographically adjacent areas intermingled and divided opinions most profoundly, especially in the areas between New York and Washington, D. C., and in the Chicago area. However, the areas selected as units comprise the results from cities as listed; the inequalities and ambiguities of our regional divisions are recognized but the results do bear contemplation. Table 2 lists the cities included in each area.

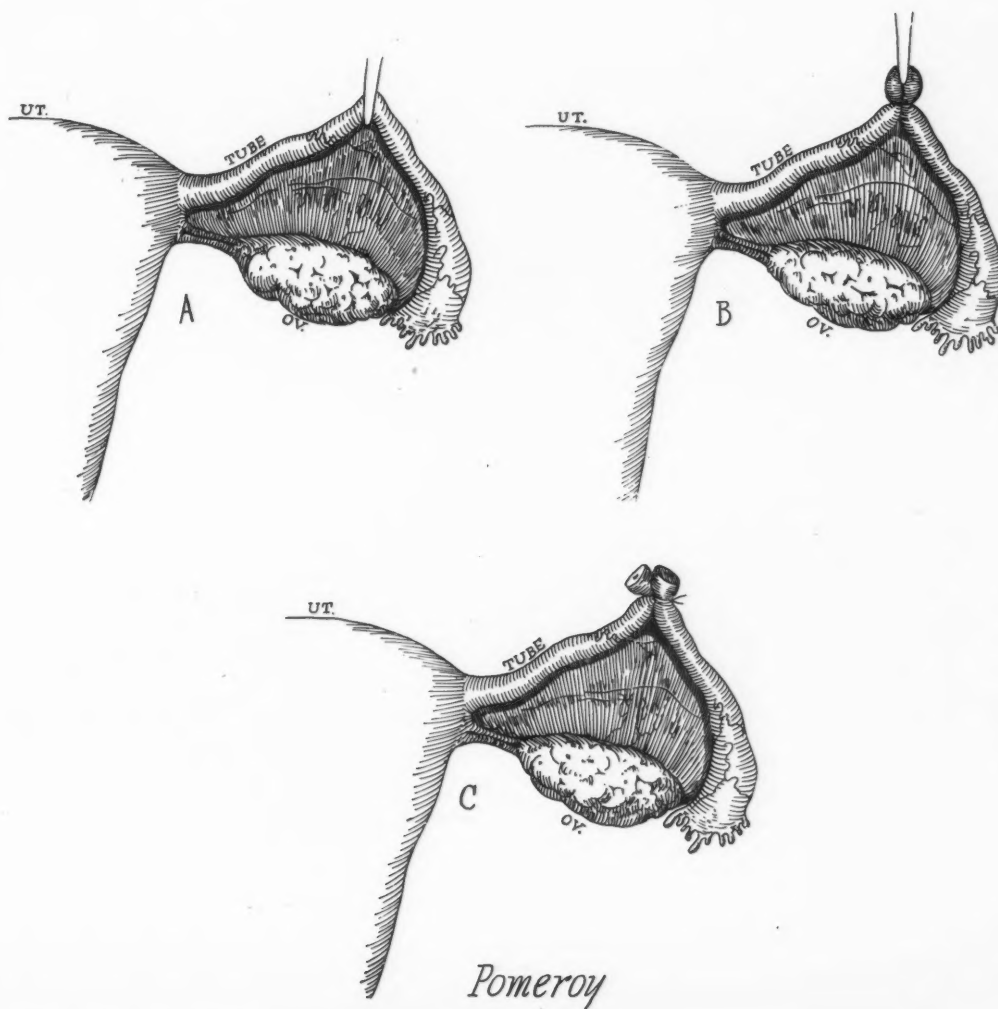
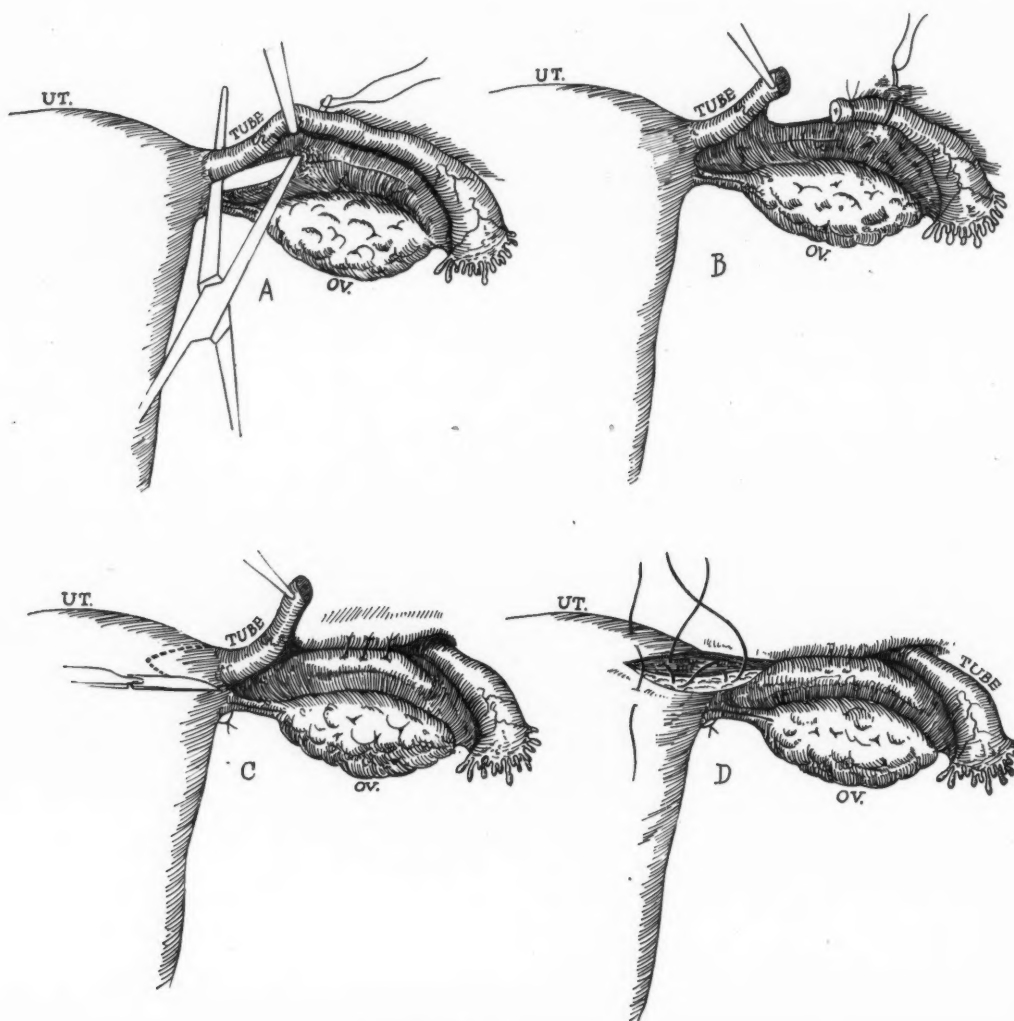


TABLE 2.—Cities in the Various Areas to Which Questionnaires Were Sent

LOS ANGELES AREA:	SOUTH:	CHICAGO AREA:	NORTHWEST AREA:
Santa Monica	Huntington, W. Va.	Indianapolis	Portland
Beverly Hills	Birmingham, Ala.	Rochester, Minn.	Vancouver
Glendale	Washington, D. C.	Milwaukee, Wis.	Seattle
Pasadena	New Orleans	Detroit	NEW ENGLAND AREA:
Los Angeles	Morehead, N. C.	Cleveland	Providence
San Diego	Charlottesville, Va.	Chicago	Manchester, Conn.
NEW YORK AREA:	Durham, N. C.	St. Louis	New Haven, Conn.
Syracuse	Nashville, Tenn.	Columbus	Boston
New York	Charlotte, N. C.	SAN FRANCISCO AREA:	MIDWEST AREA:
Englewood, N. J.	Louisville, Ky.	San Francisco	Omaha
Brooklyn	Spartansburg, S. C.	Sacramento	Oklahoma City
Jersey City	Atlanta, Ga.	Berkeley	Kansas City
Atlantic City	Augusta, Ga.	PHILADELPHIA AREA:	Iowa City
Rochester, N. Y.	Little Rock	Philadelphia	Denver
Baltimore	Miami, Fla.	Pittsburgh	San Antonio



*Cornual*



The sectional influence can be graphically emphasized. Table 3 shows the sterilization procedures chosen with cesarean section. Herein is indicated the distinct preference for the Pomeroy technique in the area surrounding New York, Philadelphia, and in the South. In and about Chicago there is a slight favorit-

ism for Madlener's method. However, the Los Angeles regional survey demonstrates an inclination toward subtotal hysterectomy not reported from other parts of the United States. Preferences from other areas varied, but it is apparent that most of the physicians who answered use either Pomeroy, Madlener, or cornual resection techniques routinely.

TABLE 3.—*Method of Sterilization Used in Various Areas in This Country (Cesarean)*

Area	Pomeroy	Madlener	Irving	Cornual	Watson	Hysterectomy Subtotal	Hysterectomy Total
Los Angeles.....	4	1	0	2	1	4	0
New York.....	17	4	0	1	1	0	0
Chicago.....	7	10	1	8	2	1	0
San Francisco.....	2	2	0	2	1	0	0
Philadelphia.....	7	3	0	0	0	0	0
South.....	11	2	1	6	0	0	0
Northwest.....	1	0	0	3	1	0	0
New England.....	2	1	2	0	0	1	0
Midwest.....	5	4	0	1	0	0	0
Total.....	56	27	4	23	6	6	0

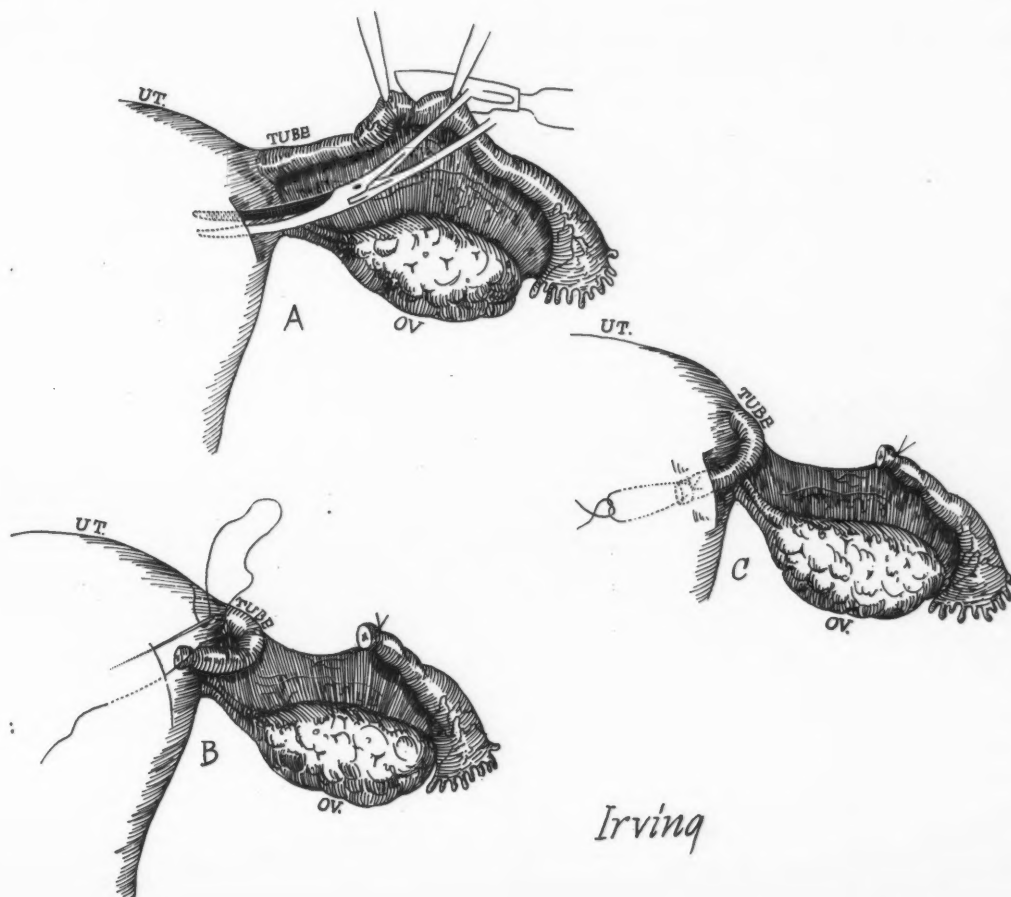
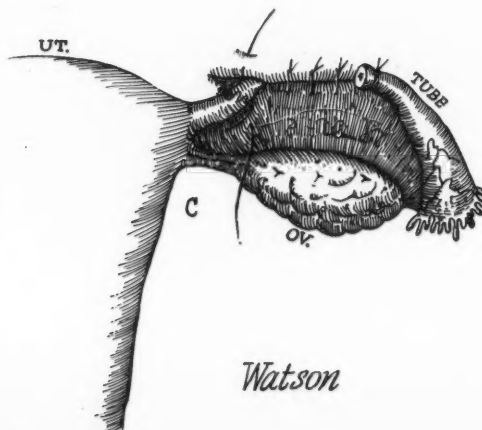
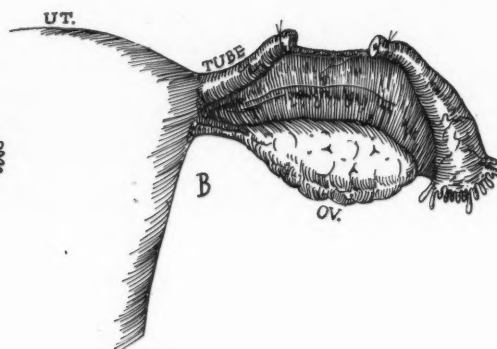
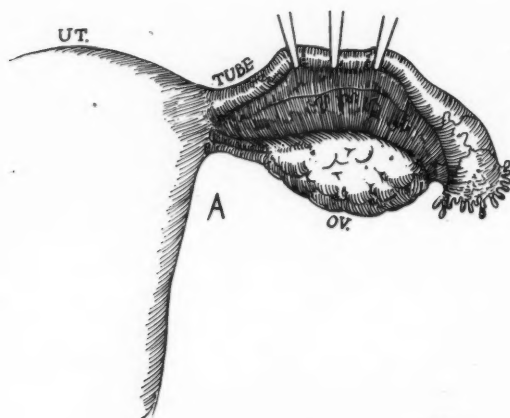


Table 4 shows the methods of sterilization used when laparotomy is done. In most instances these sterilization procedures were stated to be postpartum sterilizations. Many replies distinctly differentiated a change in technique to hysterectomy in cases in which there was a history of functional bleeding or any disease in the uterus or adnexa. Keeping in mind sterilization as the primary indication for operation, we can present the following observations. The New York area again prefers the Pomeroy method as a routine, but with increasing preference for cornual

resection. The Chicago region indicated a shift toward cornual resection as the procedure of choice. There is no change of consequence in the figures from the South, except that two who answered from that area prefer total hysterectomy exclusively; this choice is also indicated in one reply from New England. Other sections of the country appear to be about equally divided in the choice of Pomeroy, Madlener and cornual resection with the exception of the Los Angeles area where subtotal hysterectomy again takes a prominent lead.

TABLE 4.—Methods of Sterilization Used in Various Areas of This Country  
(Laparotomy)

Area	Pomeroy	Madlener	Irving	Cornual	Watson	Hysterectomy Subtotal	Hysterectomy Total	Salpingec- tomy
Los Angeles.....	2	0	0	2	1	6	0	0
New York.....	13	3	0	6	1	0	0	0
Chicago.....	6	7	1	10	2	1	0	0
San Francisco.....	0	2	0	2	1	0	0	0
Philadelphia.....	5	3	0	0	0	0	0	0
South.....	10	1	1	7	0	0	2	0
Northwest.....	0	0	0	3	1	0	0	0
New England.....	0	0	2	2	1	0	1	1
Midwest.....	3	4	0	2	0	0	0	0
Total.....	39	20	4	34	7	7	3	1



Again we repeat, many answers included comments to the effect that a hysterectomy, total or subtotal, was done if there was uterine disease; the choice of operation depended upon the indications dictated by existing conditions. These figures presented do not include hysterectomies as a sterilization procedure, unless the reply to the questionnaire indicated that sterilization was the primary reason for removing the uterus.

Many of the doctors included comments with the questionnaire. Among the most frequent of these was that cornual resection had been the procedure of choice until recently, usually about 1941, but that Pomeroy's technique is now replacing it because there is less bleeding and it is simpler and quicker.

In summary then, on this phase of our presentation, from 124 replies we found the results shown in Table 5. The Pomeroy technique is the most frequently used following both cesarean and laparotomy. Madlener's method is next most frequently used with cesarean, but the cornual resection is used more often with laparotomy.

TABLE 5.—Methods of Sterilization in the Order of Frequency of Use with Cesarean Section and Laparotomy.

	Cesarean	Laparotomy
Pomeroy.....	56	39
Madlener.....	27	20
Cornual.....	23	34
Watson.....	6	7
Subtotal Hysterectomy.....	6	7
Total Hysterectomy.....	0	
Irving.....	4	4
Salpingectomy.....	0	1

The answers to the question on the incidence of menopause symptoms within three to five years following hysterectomy in women under 30 years of age were interesting because of the diversity of opinion. Ninety-seven of the physicians returned a reply to this question, but 14 either (a) had not heard of the problem; (b) had insufficient experience to warrant an opinion; or (c) did not do hysterectomies on women under 30 years of age.

Experience among the remainder of the doctors ranged from 0 per cent to 98 per cent. It is quite apparent from Table 6 that the majority felt that there were no menopausal symptoms from the hyster-

TABLE 6.—Percentage of Patients Under 30 Years of Age Showing Menopausal Symptoms After Hysterectomy.

Answers to Questionnaire	
No opinion .....	14
0 .....	32
1 .....	12
5% .....	5
10% .....	6
15% .....	4
20% .....	5
25% .....	1
50% .....	6
75% .....	4
90% .....	3
95% and over.....	5

ectomy per se. However, five physicians thought that 95 per cent developed symptoms. To analyse a little further, 18 of the answers indicated such symptoms were present in more than 50 per cent of the patients, but 32 felt that they were present in none, and 44 replied that they were present in 1 per cent or less. One physician stated that menopausal symptoms followed cesarean section hysterectomy in only 15 per cent of the total number of cases, but that 40 per cent of the non-pregnant women developed the symptoms following hysterectomy.

Many parenthetically injected comments brought out the thought that hysterectomy is seldom done in the absence of disease. The disease which involved the tubes and ovaries caused the development of the menopausal symptoms rather than did the hysterectomy itself.

In conclusion, we recapitulate the results of our questionnaire to show:

1. The Pomeroy method of tubal sterilization is the most frequently used following cesarean section and with laparotomy.
2. The Madlener technique is the second most popular method used after cesarean.
3. Cornual resection is the second most popular method with laparotomy.
4. Hysterectomy is chosen when uterine disease exists.
5. A majority of the physicians who answered our questionnaire believe that less than 1 per cent of the women under 30 who have had a hysterectomy suffered menopausal symptoms within three to five years.

103 South Ardmore Street.

The authors are indebted to 124 physicians who showed the interest and courtesy to answer our questionnaire. The interest of Dr. Clifford Lull, who replied at length and sent reprints of his work is especially appreciated, and we are grateful also to the many who wrote their personal comments to help us evaluate their opinions.

Discussion by DONALD G. TOLLEFSON, M.D., Los Angeles

I am particularly interested in discussing sterilization from the medico-legal standpoint, for it must be constantly emphasized that the proper consent must be obtained from both the patient and her husband. This authorization blank should state that both the parties understand that the operation may render the individual sterile. This must be signed in the presence of a witness and the patient must not have had sedation within a reasonable length of time before the signing which might render her incapable of making the decision. It is also advisable to explain to the patient and her husband that the procedure cannot be undone once it has been performed. In the event that a laparotomy for pelvic disease may render the patient sterile, the couple should be informed of this possibility.

Sterilization without indication carries a real hazard to the physician from a legal standpoint, for, according to law, only the mentally ill patients committed to an institution may be so treated. While the consent of both husband and wife to an operation they have been told might make the wife sterile might seem sufficient (and no cases in this state have been tried), it is almost certain that sooner or later a physician may be called upon to explain why the operation was done.

It would, therefore, seem advisable that consultation with another physician be had whenever this procedure is considered.

It also should be brought out that the surgeon who performs the operation is responsible for his act and therefore ought not be just a technician. He must be able to justify his action with full knowledge of the facts, and not depend upon a referring physician to bear the responsibility. This is true for sterilization in either male or female.

Elective sterilization should not be treated too lightly, and some indication with a consultation of other physicians should be the rule.

This paper is interesting from several standpoints. It covers the history of sterilization techniques. It also reveals the wide variation in methods used in different medical centers of the country. The method chosen is apparently popular because of the stimulation of local outstanding physicians rather than its relative value over other types of procedure. Another point of interest is the evident marked difference of opinion among leading gynecologists as to what constitutes menopausal symptoms.

I should like to discuss the practical application of a few of the methods of sterilization mentioned. In 1938 I became acquainted with Robert Kimbrough in Philadelphia. He was using the Lull-Pomeroy technique at that time and had had a series of two hundred cases without a failure. I was struck with the simplicity of the procedure in comparison with cornual resection, especially at the time of cesarean section. To stop the venous bleeding from the broad ligaments in doing cornual resection not infrequently took longer than the cesarean section. Since that time I have used the Lull-Pomeroy technique exclusively. It is not only an excellent means of sterilization with cesarean but it is also well adapted to the vaginal approach and the small, early post-partum, abdominal incision.

I am not an advocate of sterilization by hysterectomy in young women. An occasional failure or the rare development of a case of functional bleeding, following partial tubal resection is still on the whole preferable to the psychogenic or actual menopausal symptoms following subtotal hysterectomy. The wide variation in the percentage of menopausal symptoms following hysterectomy reported in the paper only indicates the difficulty in evaluating the importance and severity of such symptoms. I firmly believe that the patient should be given the benefit of the doubt and the menstrual function maintained whenever possible in women under the age of 36.

In cases where hysterectomy and sterilization are medically and legally indicated there is a place for fundectomy. The wedge-shaped excision of the fundus including the interstitial portion of each tube, allows the removal of the uterine contents and tubal interruption through one incision in the uterus. The soft tissue allows good peritonization.

In women approaching 40, I believe subtotal hysterectomy following cesarean section is the method of choice for sterilization purposes. Morbidity is less than with cesarean section and tubal ligation, the convalescence is shorter and the result more positive.

I have reviewed 27 cesarean hysterectomies performed during the past three years. The follow-up records reveal very satisfactory results on the whole. Nine of the patients menstruate for one day. All but one of these nine have stated that they wish I had stopped the process entirely. The other 17 have no different symptoms than the ones who menstruate.

In conclusion, I believe that the reported results of the Lull-Pomeroy technique of sterilization warrant its continued use in preference to subtotal hysterectomy in women under the age of 36. Fundectomy is the operation of choice in cases requiring hysterotomy and sterilization. Beyond the age of 36 the uterus can be removed at the time of cesarean as a means of sterilization with good results.

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## The Diagnosis of Scleroma

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**R**HINOSCLEROMA was first described in 1870 by von Hebra.<sup>14</sup> He considered it an unusual form of skin cancer. Geber<sup>3</sup> recognized the lesion as a chronic inflammatory process accompanied by perivascular cellular infiltration and connective tissue proliferation. Mikulicz<sup>9</sup> described the histological picture which is now recognized as being characteristic of the disease. The "foam" or "lace" cells seen in this granuloma bear his name.

As the disease is not confined to the nose as von Hebra originally assumed in using the prefix "rhino," the more inclusive term "scleroma" was officially adopted at the Second International Congress of Otorhinolaryngology<sup>11</sup> held in Madrid in 1932.

### INCIDENCE

Scleroma was once thought to be confined to Central and Southeastern Europe, but it is now recognized more often and is generally acknowledged as world-wide in occurrence. In a comprehensive report, Cunning and Guerry<sup>1</sup> in 1942 reported that 102 cases had been described to that date in the American and Canadian literature. Streit<sup>13</sup> contends that an endemic area exists in Central Europe, especially Poland. Lasagna<sup>6</sup> feels that it is becoming more common in Italy, and there is some evidence that the disease is seen frequently in Central and South America.

### PATHOLOGY

Scleroma is a chronic disease of the upper air passages involving the mucosa and submucosa. Clinically, three stages are described. The first stage resembles atrophic rhinitis with profuse secretion, crust formation and foul smell. The second stage is characterized by proliferation of tissue which leads to obstruction of the air passages. In the third stage there is cicatrization and stenosis causing marked deformity. The lesion usually starts at the anterior portion of the nostril in the mucosa. It may extend anteriorly and involve the skin in the vestibule and around the aperture of the nares. The lesion also progresses posteriorly involving the turbinates, pharynx, soft palate, uvula, pillars, larynx and trachea.

This disease is apparently transmitted by long contact under poor hygienic environment. No facts are available regarding the incubation period. The onset is insidious and the duration may be from 20 to 30 years. There is little effect on the general health except for the mechanical obstruction of the air

passages which in extreme cases may lead to death by asphyxia.

The lesions may be classified in three types which roughly parallel the three clinical stages. In the earliest lesions gross examination shows atrophy of the mucosa with crust formation. Ulceration may result from trauma due to the atrophic epithelial covering. The microscopic appearance of the early lesions is not sufficiently characteristic to lead to a diagnosis of scleroma. In areas normally covered with stratified squamous epithelium there is atrophy of the middle layers (stratum lucidum and stratum granulosum) and disappearance of rete pegs; although there may remain an occasional irregularly shaped hypertrophied rete peg. The epithelial covering is thinned to two or three cell layers in thickness. There is regular arrangement of the basal layer of epithelial cells. In areas normally covered by ciliated columnar epithelium there is a multiplication of cell layers forming ciliated stratified columnar epithelium which later by metaplasia becomes atrophic stratified squamous. Covering the epithelial surface there is a crust formed of dried mucus and necrotic exudate. The pictures in the corium and submucosa are similar. There may be a narrow zone immediately beneath the epithelium which is comparatively free of inflammatory changes. Beneath this there is a granuloma of non-specific nature. The fibroblasts and capillaries are masked by the dense infiltration with wandering cells. The exudate consists chiefly of plasma cells but there are also lymphocytes, polymorphonuclears, mononuclears and histiocytes. Mikulicz cells are not present in sufficient numbers to attract attention.

The proliferative phase is not sharply defined from the atrophic. Nodules varying from 1 to 10 mm. in diameter occur singly or in groups. These, when first developed, are soft, later become hard. This tissue may completely fill the nasal passage from the nostril to the nasopharynx. When the larynx or trachea is involved, the proliferative lesion may lead to asphyxia. The facial appearance is sometimes markedly disfigured by the nodular lesions protruding from and surrounding the nasal orifice. The microscopic appearance at this stage is that of a chronic granuloma. The surface may be covered by atrophic stratified squamous epithelium without rete pegs or with a few hypertrophied distorted rete pegs. Part of the surface may be ulcerated and covered by a crust of necrotic exudate. The submucosa is replaced by a thin zone of collagenous tissue and granulation tissue composed of young blood vessels and fibroblasts. Beneath this zone the granulation tissue is filled with a dense infiltrate of plasma cells,

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Read before the section on Pathology and Bacteriology at the 76th Annual Session of the California Medical Association, Los Angeles, April 30-May 3, 1947.

lymphocytes and mononuclear cells. Colloid or hyaline cells with deeply acidophilic cytoplasm and small, darkly stained, eccentric nuclei and also a few Russell fuchsin bodies may be seen scattered throughout the granuloma. The cell most characteristic of this lesion is the Mikulicz cell. However, it may be found at times in granulomas of other types also. This cell is 15 to 20 times the size of a red cell, has a large clear vacuole and a small eccentrically placed nucleus on the cell membrane. Such cells may be scattered throughout the granuloma or they may occur in large groups forming foamy appearing, light staining areas. Frisch bacilli may be found in the vacuoles or in interstitial spaces around these cells. Collagenous connective tissue usually separates the granuloma from the underlying cartilage or bone.

In the stage of cicatrization there is marked distortion of involved structures. The tissue consists of hard, tough scar. Microscopically the section shows a disorderly array of heavy collagenous fibers with relatively few connective tissue nuclei. Here and there one may find irregular areas darkened by aggregations of pyknotic nuclei. A few atrophic gland acini are seen scattered through this scar tissue. An occasional island of granulation tissue or group of Mikulicz cells may be found. Bacteria are difficult to demonstrate in the section during this stage but can be recovered in cultures. The histological picture of this final stage of scleroma is not sufficiently characteristic to lead to a diagnosis without supporting evidence.

#### BACTERIOLOGY

We consider *Klebsiella rhinoscleromatis* to be the cause of scleroma. The organism was described by Frisch in 1882, and was asserted by him to be the causative agent. It is a short, plump Gram-negative bacillus, growing readily on ordinary culture media, where it forms mucoid, spreading colonies 2 to 5 mm. in diameter which become confluent when crowded. Fermentation of carbohydrates is characteristic: dextrose, maltose and mannite are fermented without production of gas. Lactose is not fermented, while sucrose is attacked slowly by some strains. Indole is not formed.

The reluctance of many workers to accept the bacillus of von Frisch as the causative agent is due in part to the failure to reproduce the disease in the experimental animal, and to the alleged appearance of the bacterium in the respiratory passages of healthy persons. In a study reported elsewhere<sup>7</sup> we found that *K. rhinoscleromatis* did not appear in the respiratory tract in 267 individuals. The Friedlander's bacillus (*K. pneumonia*) may be mistaken for *K. rhinoscleromatis* upon superficial examination, but the carbohydrate fermentation pattern distinguishes these two forms readily. *K. pneumonia* regularly ferments lactose and sucrose, and most strains produce gas in addition to acid.

A satisfactory procedure for the isolation of *K. rhinoscleromatis* from the respiratory tract of a suspected case is as follows:

Culture material from nose and throat are streaked heavily or smeared on eosin methylene blue plates. This inhibits the

growth of Gram-positive microorganisms and favors the growth of the Gram-negative group. Plates are observed after 24 and 48 hours' incubation. Translucent mucoid colonies are subcultured again on E.M.B. streak plates, and isolated colonies are picked to agar slants. When microscopic examination indicates the culture to be pure, carbohydrate broth tubes are inoculated. Readings are made at 24 and 48 hours. Strains fermenting dextrose, maltose and mannite with acid only and showing no reaction on lactose or sucrose are considered to be *K. rhinoscleromatis*.

These observations agree with those of Figi and Thompson,<sup>2</sup> and of Morris and Julianelle,<sup>10</sup> as well as with the less detailed reports of Gonsiorowski and Meisel.<sup>5</sup>

A possible source of confusion lies in the difficulty in obtaining pure cultures. Due to the mucoid, spreading nature of the colony, contaminants may be incorporated into the growth which are hard to eliminate. Usually repeated streaking on E.M.B. plates will eliminate the contaminant.

#### SEROLOGY

The details of the complement-fixation test for scleroma appear elsewhere.<sup>8</sup> The antigen used in this test is a strain of *K. rhinoscleromatis* isolated from a patient having scleroma. After cultivation for seven days in nutrient broth containing 5 per cent dextrose, the bacteria were removed by centrifuging. The supernatant liquid was discarded and the bacilli were washed in 0.85 per cent saline solution. A heavy suspension of the washed organism was made, exposed to a temperature of 65° C. for 30 minutes and suspended in a solution of Merthiolate (1:5000) in 0.85 per cent sodium chloride. The anticomplementary titre of the suspension was determined, and the final dilution of the antigen was made to give a negative antigen control. The actual titration was carried out according to the method of the quantitative Kolmer Wassermann.

Using the methods just described, 11 sera from patients with scleroma gave strongly positive reactions in relatively high dilution. A total of 534 sera from individuals not having scleroma were tested in the same way. Of these, 15 or 2.8 per cent gave positive reactions. All but two of these 15 showed a titre of less than 1:10. Additional work is needed to establish the test, but we feel that on the basis of the evidence submitted the complement-fixation test, if the result is positive, is of considerable value in establishing a diagnosis. The possible occurrence of negative results in early cases of scleroma must await further study.

#### CASE STUDIES

One further controversial question concerning scleroma has been its contagiousness. Its endemic nature has been suggested previously. Familial occurrence would indicate an infectious trait. Lasagna,<sup>6</sup> Robertson and Secretan,<sup>12</sup> and Gerber<sup>4</sup> have reported duplicate cases occurring in the same family. We have studied seven cases, six of which have occurred in the same family.

CASE 1.—A 20-year-old male of Mexican descent was referred to the clinic because of dyspnea and a cough productive of a thick yellow mucoid material.

About one year before he had begun to notice that his nostrils were "plugged up" and that a sticky yellow discharge was chronically present. The significant physical findings related to the respiratory tract. A hard granulomatous mass filled the nares, nasopharynx, and the pharynx. In some places the mass was covered by dirty, green, malodorous crusted material which was occasionally expectorated. The voice was hoarse and there was some granulation involving the epiglottis and aryepiglottic folds. The patient complained that the dyspnea interfered with normal activity. There were no other significant laboratory or physical findings.

Biopsy of the lesion was taken from the middle turbinate. Thin stratified squamous epithelium without rete pegs or papillae covered a granuloma composed of loosely arranged fibroblasts and newly formed capillaries. A large proportion of the granuloma was made up of diffusely scattered Mikulicz cells giving the section a lacy appearance. The cellular infiltrate consisted of many plasma cells, a few lymphocytes and mononuclears and an occasional polymorphonuclear. Numerous Russell bodies and hyaline cells could be seen. Numerous bacilli could be demonstrated extra- and intracellularly by special stains. This picture was characteristic of the proliferative stage of scleroma.

From the above patient we isolated the scleroma bacillus in 20 consecutive throat cultures on blood agar and E.M.B. agar. The organism grows as a large, mucoid, flowing colony easily picked from the usual throat contaminants after 24 hours of incubation.

On questioning this first patient, we found that his father had similar symptoms, of longer duration. A report of the father follows:

CASE 2.—The patient was 37 years of age. He had been essentially well until his nose was broken about ten years ago. After this his nose became progressively "stuffy" and a thick yellow discharge developed. Rhinoscleroma was diagnosed clinically elsewhere one year after onset and x-ray therapy was given. At the time of our examination, there was adequate airway, but the lining of the nose and pharynx was hard, irregular, and studded with foul-smelling, greenish crusts.

Biopsy taken from a warty growth on the pharyngeal wall showed a network of squamous epithelial cells enclosing cross sections of papillae. The epithelial cells were quite large with small dark staining nuclei and very prominent intercellular bridges. The papillae contained small capillaries, Mikulicz cells, a few lymphocytes, plasma cells and an occasional Russell body.

Two months after the above described biopsy was taken, considerable tissue was removed from the nose to reestablish airway which had become obstructed. Sections were made from tissue removed from the middle turbinate, posterior nares and lateral wall of the pharynx. These sections showed the cicatricial changes of the final stage of scleroma. There was atrophy of the epithelium which was stratified squamous. The submucosa was replaced by heavy collagenous fibers in a disorderly arrangement. There were a few atrophic mucous glands. One of these sections showed some granulomatous tissue with Mikulicz cells but almost all of the granuloma had been replaced by sclerotic tissue. Frisch bacilli were repeatedly isolated from cultures of the nose and throat.

After seeing that the father and son both were suffering from the same disease, we thought that other members of the family might show symptoms of a similar nature. From our discussion with father and son, we knew that they were suffering from vague symptoms associated with the upper respira-

tory tract. In addition to the son (Case 1) the family consisted of four daughters, a young son, aged nine, and the wife of the oldest son (Case 1). The mother of the children had been separated from the family for the past four years and was not available.

The wife of the patient in Case 1 and the youngest son were free of symptoms and culturally negative. The four girls seemed to show various stages of an infection of the nasopharynx which resembled the "diffuse" type of scleroma described by Szmurlo, and mentioned previously. Their case histories follow:

CASE 3.—A girl, aged 19, was asymptomatic except for frequent "head colds" and a watery nasal discharge which had been chronically present for two years. There was marked atrophy of the inferior and middle turbinates and the nose contained crusts and casts of green-yellow matter that had the same foul odor noticed in others of her family.

Biopsy sections showed a granuloma infiltrated with a few lymphocytes, plasma cells, mononuclear cells and eosinophiles. There were numerous hyaline cells and a few isolated Mikulicz cells. Most of the surface was covered with stratified sciliated columnar epithelium. Numerous mucous glands were present. Characteristic organisms were isolated from cultures of the nose and throat.

CASE 4.—The patient, a 17-year-old girl, was asymptomatic except for a chronic cough which she attributed to a thick, sticky, nasal and postnasal discharge. She had had "lobar pneumonia with empyema" three years ago and recovery had followed open drainage. Physical examination of the upper respiratory tract showed marked atrophy of the inferior and middle turbinates with some thickening of the septum superiorly and anteriorly, and the presence of greenish crusts.

Biopsy was taken from the anterior tip of the middle turbinate. The slightly irregular surface was covered on one side by stratified squamous epithelium, on the other by stratified ciliated columnar epithelium. There were many glands surrounded by loose connective tissue. The gland acini were small, the cytoplasm was pink and somewhat granular and the nuclei were small and dark. The lumina of the glands were small and appeared empty. There was moderate infiltration with plasma cells, lymphocytes and eosinophiles. There were a few vacuolated cells which possibly were Mikulicz cells. Characteristic organisms were isolated from cultures of the nose and throat.

CASE 5.—The patient, a girl of 14 years, complained of increased nasal "stiffness" of 18 months' duration, with no visible discharge. Physical examination showed almost complete obstruction due to the involvement of the anterior and of the inferior turbinates. The hypertrophied tissue causing obstruction had the appearance of granulation tissue and bled easily on touching. There was some crusting due to greenish yellow purulent exudate.

Biopsy was taken from the vestibule. The tissue consisted of a granuloma densely infiltrated with plasma cells. There were also some lymphocytes and neutrophils. The surface was covered with a crust of necrotic exudate. There were a few islands of squamous epithelium beneath the crust. A few vacuolated cells, possibly Mikulicz cells, were present. The picture was that of a nonspecific granuloma. Repeated cultures showed the presence of scleroma bacillus. The lesion was that of early scleroma.

CASE 6.—The patient was an 11-year-old girl who was asymptomatic although her sisters complained that she was always clearing her throat. Examination showed considerable hypertrophy of the tonsils. No atrophy, granulation or crusting was present in the nares.

(There is no record of a biopsy having been taken.)

The findings in the last four cases, in our opinion, present pictures resembling varying stages of rhinoscleroma. In none of these cases were the symptoms sufficiently severe to result in the patient being referred to a doctor, yet physical examination revealed lesions which, at least in three of the cases, were suggestive of the disease. In one patient, the youngest sister, there were practically no gross pathologic lesions. The microscopic picture in all the other cases confirmed the existence of the disease syndrome, which, together with the isolation of the scleroma bacillus in each case, gave extremely presumptive evidence that here we had a family in which six members were afflicted with various stages of the disease rhinoscleroma. Serological findings in each of these cases gave further supporting evidence, although until the complement-fixation test, mentioned previously, is standardized, emphasis on the serology must be avoided.

#### SUMMARY

Scleroma is an infectious disease which is endemic in Southern California and must be considered in diagnosing lesions of the respiratory tract. The diagnostic procedure includes bacteriological, serological, and histological examinations. The bacteriological findings are positive in all stages of the disease. In early cases of scleroma the histologic appearances may not be pathognomonic. Identification of early scleroma by serologic tests has not been worked out. All of the advanced cases studied have been found to give positive reactions to complement-fixation tests. The proper evaluation of the information revealed by these three tests is diagnostic.

*Discussion by H. JAMES HARA, M.D., Los Angeles*

Six of the seven patients mentioned in this paper I have seen. These six patients are one family—father, son and four daughters. They were all born in Colorado of Spanish, French, Indian, and Mexican ancestry and have lived in California since 1942. I know of no other instance in which there were so many cases in one family.

From 1893 to date 104 cases have been reported in the literature in the United States and one from Canada. Sixteen of the patients were born in the United States.

Clinically, two types are recognized. In the first group the characteristic lesion is a chronic granuloma invading the mucous membrane of the respiratory tract. The initial site of invasion is usually in the nose and progressively spreads to the nasopharynx, pharynx, larynx, trachea, and even to

the bronchus. In some instances the larynx has been reported to have been the site of the primary lesion. In the second group the conspicuous lesion is in the skin area of the nasal vestibule, extending into the upper lip and protruding fairly firm masses without ulceration over the lower portion of the external nose. The lesions begin in the mucous membrane of the nose as a chronic granuloma and spread to the skin.

Three diagnostic criteria are:

1. Culture and isolation of Frisch organism.
2. Complement fixation.
3. Biopsy in later stage.

With the aid of laboratory workers scleroma can be accurately recognized long before the clinical diagnosis is possible.

Streptomycin is the specific: 0.5 gm. is given as an aerosol inhalation. Two gm. daily intramuscularly in four divided doses are given each day for 10 days. In one of our patients the organism disappeared on the seventh day.

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# CASE REPORTS

◀ Eosinophilic Granuloma of Bone with Diffuse Pulmonary Involvement      ▶ Dissecting Aneurysm

## Eosinophilic Granuloma of Bone with Diffuse Pulmonary Involvement

DOUGLAS D. DICKSON, M.D., *Oakland*

IT is possible that Hand-Schuller-Christian's Disease, Letterer-Siwe's Disease and eosinophilic granuloma represent different phases of similar pathologic entities.

Various explanations have been given as to the etiology of this group of diseases. Rowland's studies<sup>7</sup> in 1928 led him to believe the causative factor was disturbed lipid metabolism. Sosman<sup>8</sup> also classified xanthomatosis as a disease of lipid metabolism. Jaffe and Lichtenstein<sup>4</sup> have concluded from their studies that eosinophilic granuloma of bone, Letterer-Siwe's Disease and Hand-Schuller-Christian's Disease may be considered different clinico-anatomic expressions of the same disease.

Green and Farber<sup>2</sup> point out the similarity between roentgenographic and histopathologic findings demonstrated in Hand-Schuller-Christian's Disease, Letterer-Siwe's Disease and eosinophilic granuloma.

In four of Rowland's cases of xanthomatosis, (Hand-Schuller-Christian type) that came to autopsy, a marked degree of pulmonary fibrosis was observed. Currans and Popp<sup>1</sup> report a case of xanthomatosis (Hand-Christian-Schuller type) with pulmonary fibrosis.

Imler<sup>3</sup> reports two cases of eosinophilic granuloma (reticulo-endotheliosis) with pulmonary manifestations, one of which represented the Hand-Christian-Schuller type.

Pulmonary lesions secondary to eosinophilic granuloma must be a rare manifestation of a fairly common disease. Numerous case reports of eosinophilic granuloma without the pneumonic lesions have been reported since Jaffe and Lichtenstein<sup>5</sup> and Otani and Ehrlich<sup>6</sup> almost simultaneously described the new entity.

Following is a case report of eosinophilic granuloma with pulmonary manifestations.

### CASE REPORT

A 30-year-old white male was first examined in June, 1946. Four years previously there had been an injury to the left shoulder. In 1942 roentgenograms of the left shoulder revealed a cystic lesion of the acromion. (These roentgenograms were made elsewhere.) Symptoms subsided in a few days. Shortly thereafter, the patient applied for admission to the armed services and was rejected for "silicosis." For one year before our examination there had been pain along the inner side of the left thigh. One month before examination, dull aching pains in the region of the left hip had begun.

There was no history of exposure to silica. The patient was a healthy appearing white male and, except for tenderness overlying the left greater trochanter, physical examination disclosed no abnormalities.

Specific gravity of the urine was 1.016. There was no albumin or sugar and results of microscopic examination were negative. A Bence-Jones protein determination was normal.

Erythrocytes numbered 4,450,000 and leukocytes 10,550 for each cubic millimeter. There were 1 stab and 59 segmented neutrophils, 39 lymphocytes, and 1 eosinophil. The sedimentation rate was 18 mm. in 1 hr. 5 min. A sternal puncture\* revealed increased eosinophils. Result of a Wassermann test

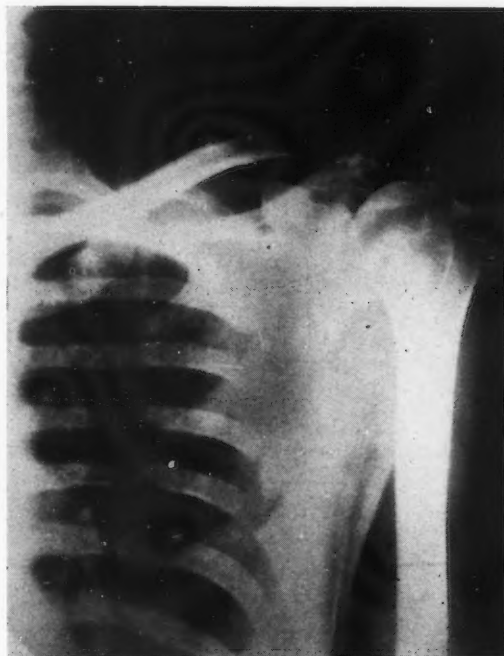


Figure 1. Anterior-posterior x-rays of the left acromion demonstrating cystic changes in the acromion process.

was negative. Serum calcium was 11.4 mg. per cent and serum phosphorus 3.5 mg. per cent. Acid phosphatase was 2.0 King-Armstrong units and alkaline phosphatase 6.8 King-Armstrong units. Serum albumin measured 5.27 gm. per cent and serum globulin 1.63 gm. per cent. Electrocardiographic tracings were within normal limits. Roentgenograms (Figures 1 and 2) revealed cystic areas in the left acromion, in the first sacral segment, in the ischium about the acetabulum and in the region of the left greater trochanter.

On the right, cystic areas were present in the ischium. There was also a destructive lesion in the adjacent margins of the 12th thoracic and first lumbar vertebra.

Chest films (Figure 3) revealed a diffuse infiltration of both lung fields. There were a few Gram positive rods in the sputum, numerous pus cells and rare eosinophils.

A biopsy was done on the lesion of the left femur. Yellowish gelatinous material was encountered. Microscopic sections (Figure 4) showed the tissues to be made up of connective tissue cells, some of which contained vacuoles in which lipid material had been deposited. These connective tissue cells (histiocytes) gave a granulomatous appearance to the tissue. Eosinophilic leukocytes were present in enormous number, and there was an occasional giant cell. Numerous areas of necrosis were present in the section.

\*We are indebted to Dr. Ernest Falconer for his opinion with reference to the examination by means of sternal puncture.

From August 6 to September 2 x-ray therapy was given to the lesion involving the left shoulder, the right lung, the left ilium and the left upper femur, administered in the following manner.

Right anterior chest: Field 15-17 cm. 200 k.v.p., (Filter  $\frac{1}{2}$  mm. cu. and 1 mm. al.). Skin target distance 70 cm. Four treatments totalling 1014 r.

Left shoulder posterior portion: Field 15-17 cm. 200 k.v.p. ( $\frac{1}{2}$  mm. cu. 1 mm. al.). Skin target distance 70 cm. Six treatments totalling 1014 r.

Left ilium and left upper femur: Field 15-17 cm. 200 k.v.p. (Filter  $\frac{1}{2}$  mm. cu. 1 mm. al.). Skin target distance 70 cm. Six treatments totalling 1014 r.

Roentgenographic examination of the chest on October 29, 1946, revealed no improvement so far as the lungs were

concerned. However, marked improvement could be demonstrated in the roentgenogram of the ilium and the left femur, with considerable evidence of sclerosis of the cystic areas,



Figure 2. Anterior-posterior x-rays of pelvis demonstrating cystic lesions in the ilium and left greater trochanter.

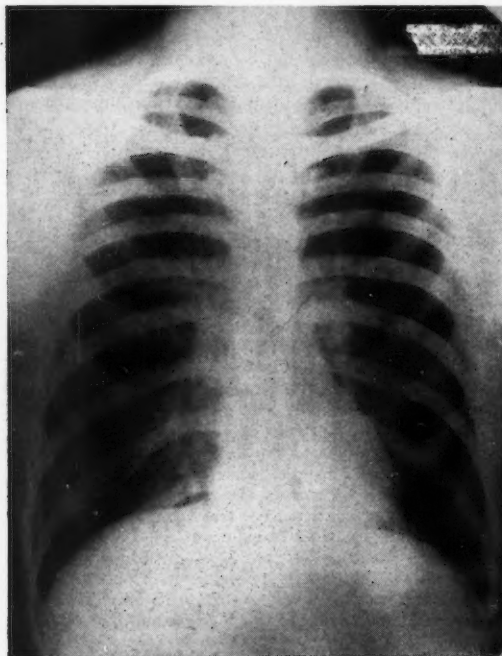


Figure 3. Anterior-posterior x-rays of the lungs revealing diffuse infiltration of both lung fields.

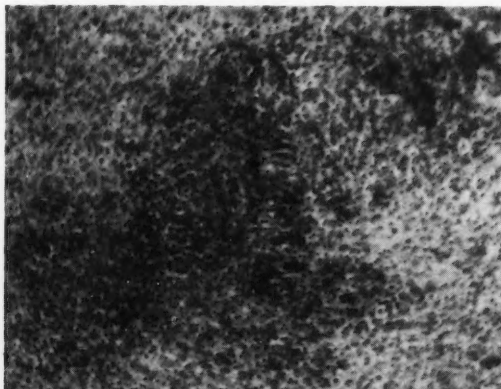


Figure 4. Microscopic examination of tissue removed from left greater trochanter revealing histiocytes and eosinophilic leukocytes.



Figure 5. Anterior-posterior x-rays of the left ilium and left greater trochanter demonstrating the regeneration of bone at the site of the cystic areas involving the ilium and left greater trochanter following x-ray therapy to the ilium, and excision and transplantation of iliac bone chips to the cyst in the left greater trochanter.

both in the ilium and the left greater trochanter (Figure 5).

This case has been reported because of the pneumonic manifestations associated with extensive osseous lesions characteristic of eosinophilic granuloma.

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### Dissecting Aneurysm

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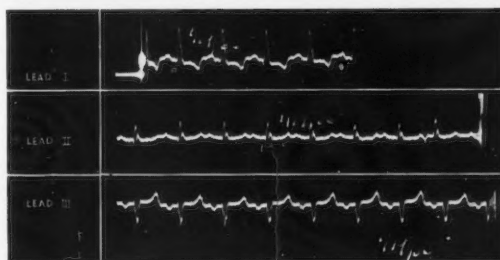
**D**ISSECTING aneurysm of the aorta rivals syphilis in the number and variety of disease entities which it may simulate, and with which it may be confused. It occurs more frequently in men than in women, and usually in patients with preexisting hypertension. Erdheim's medial necrosis is the primary lesion in some cases, and dissection results by virtue of hematoma formations within the wall of the aorta. Primary rupture of the intima and subsequent dissection of the media also occur in the absence of preexisting medial necrosis.

The diagnosis is made by the location of the pain, which is often excruciating. It frequently resembles distress in the chest produced by coronary thrombosis, but does not radiate to the arm. It does tend to radiate to the back, between the scapulae, and sometimes to the neck and head, lower back and legs. It may be throbbing in character and intermittent. The physical findings are variable. The blood pressure does not drop, unless the patient develops the signs and symptoms of shock. The sudden development of a diastolic murmur of aortic insufficiency accompanied by the increased pulse pressure may appear. Roentgenography and fluoroscopy of the chest are most helpful, showing a widening of the aorta, especially in the oblique view. The electrocardiogram does not change materially. The Wassermann reaction, when positive, serves more often than not to confuse the diagnosis. The prognosis is somewhat better than in the case of coronary thrombosis if outcome is not immediately fatal. The treatment consists of rest in bed during the acute stage with repeated doses of morphine.

#### CASE REPORT

The patient, a woman aged 71 years, on October 15, 1934, ate half a watermelon and a whole chicken at one meal. She awoke the next morning in a clammy sweat with severe sharp pain in the upper left thoracic region posteriorly. Heart sounds were regular but distant. The blood pressure was 112 mm. systolic and 76 mm. diastolic; three days later it was 202 mm. systolic and 112 mm. diastolic. Urinalysis showed 2 plus albumin with hyaline and granular casts. The

Wassermann reaction was positive. On October 23 erythrocytes numbered 4,080,000, with hemoglobin 57 per cent, and leukocytes numbered 8,950. The non-protein nitrogen on October 17 was 43.8 mg. per 100 cc., and on October 21 was 65.3 mg. per 100 cc. The blood sugar on October 17 was 160.0 mg. per 100 cc. and on October 21 was 85.4 mg. per 100 cc. Later determinations of the blood sugar were persistently high. On November 20, a roentgenogram showed a large aneurysm of the ascending aorta and of the arch of the aorta present with enlargement of the heart (Figure 1). An electrocardiogram showed inverted T1 (Figure 2). The non-protein nitrogen remained elevated. Much pus appeared in the urine on February 12 with accompanying rise of temperature, pain and tenderness in the right side of the abdomen. Vomiting was severe. A mass was felt by bimanual examination in the right lower quadrant of the abdomen.



A hemorrhagic ovarian cyst was the diagnosis. The leukocyte count was elevated to 16,900 with 89 per cent polymorphonuclear cells, of which 55 per cent were early forms. Vomiting persisted. Edema appeared. The patient became more and more stuporous and finally died March 8, 1935. Through the course of the illness, there was some precordial distress but none as severe as at the time of the onset.

Anatomical diagnosis\*: healing dissecting aneurysm of aorta; medial necrosis idiopathica cystica of Erdheim; high grade atherosclerosis of aorta and major branches; benign nephrosclerosis; generalized arteriolar sclerosis (hypertension); marked hypertrophy and dilatation of heart; obliterative fibrous pericarditis; generalized passive congestion; anasarca moderate; high grade cerebral sclerosis; softening in left parietal cortex and in right lobe of cerebellum; chronic

\*By Dr. Alvin Foord, Pasadena.

periappendiceal abscess well walled-off; purpuric hemorrhages in skin; atrophy of thyroid; obesity chiefly girdle type in distribution; diverticulum of sigmoid; steatosis of pancreas; small area of necrosis in pancreas (vascular in origin); chronic cystitis and pyelonephritis; cyst of right ovary; fatty infiltration of liver.

The heart was markedly enlarged and measured in the fixed specimen 12 cm. across and 13 cm. in length. The apex was formed exclusively by the left ventricle. There was considerable dilatation of all the chambers. The valves were free from change. Congenital defects were absent. The pulmonary and aortic orifices were markedly dilated. There was no evidence of fibrosis in any part of the organ, nor was any fresh necrosis seen. The left ventricle muscle was profoundly hypertrophied and measured from 15 mm. at the apex to 25 mm. at the base. The right ventricle muscle was only 3 to 4 mm. There was a large amount of fat in the epicardium, which extended somewhat into the muscle. The coronary vessels were very large, the left main coronary showing a lumen fully 6 mm. in diameter, and the major trunks were hypertrophied, consistent with the size of the heart. There were a few calcified plaques and a diffuse stiffening but no evidence of any encroachment upon the lumen, and no thrombosis was present.

Of particular interest was the aorta. The ascending portion and the arch showed much dilatation, and a baseball easily could have been put in the pocket just above the aortic valve. The intima, however, was glistening and smooth, and there were none of the ordinary signs of lues in this portion. The aortic leaflets were free from involvement and were soft and pliable. Just at the arch and to the right was a sacculated portion with an orifice about 4x4 cm., forming a mass about the size of half an egg, which was filled with organized blood clot. A smaller, similar dissecting pocket was noted on the posterior wall about the level of the origin of the innominate artery, forming a sac about 2x1 cm. The edges of both of these pockets were rolled and perfectly smooth and glistening and almost of the consistency of cartilage. Just above the left leaflet of the aortic valve was a third pocket showing dissection with pocket formation within the wall of the aorta, measuring about 2x2 cm. From this extended a crevice where the intima had obviously been separated and the defect filled in with a pink or white scar tissue, extending upward for a distance of about 8 cm., and from this similar evidence of old tears extended into the two pockets just described. The intima above these was smooth and glistening, and there was practically no plaque formation. There were numerous atheromatous and hyaline plaques at the arch and particularly at a point just below the arch, where an egg-shaped sacular aneurysm about 2 cm. deep was found. This measured about 5 cm. in diameter, the wall was thin, and the surface was covered by organized thrombus. Calcium plaque formation was found in this portion. Evidence of old laceration of the intima extended transversely and practically around the aorta at this level. Below this the aorta was diffusely dilated, tortuous, showing some longitudinal wrinkling, but primarily large yellow and hyaline plaques with small areas of calcification. Below the diaphragm there was profound tortuosity and not much dilatation. The major branches showed also profound tortuosity, marked plaque formation, and some calcification. The circumference at the extreme arch was about 9 cm. and at the diaphragm 7 cm.

#### COMMENT

Taylor and Morehead discussed the rupture of the aorta which occurs without the formation of a dissecting aneurysm. This occurs more frequently than is usually realized. Ash suggests that the study of the circulatory changes in the right arm with the observation of superior mediastinal obstruction and absence of pulse in the right carotid and right subclavian

arteries leads to the correct diagnosis and localization of the lesion. Wainwright comments on the present-day tendency to diagnose as coronary thrombosis all conditions even remotely simulating it. Such a condition might well be a dissecting aneurysm. He reports an instance of coronary dissection resulting in occlusion of the vessel with a diagnosis of dissecting aneurysm before death. Ritvo and Votta commented on the value, in establishing the diagnosis, of roentgen studies showing increase in the width of the shadow of the aorta, cardiac hypertrophy, pericardial effusion and fluid in the pleural space. Leonard stated that the dictum was that "dissecting aneurysms caused by trauma are rare" but he presents a case of a patient who had one following an automobile accident. He said that the diagnosis of dissecting aneurysm must be differentiated between coronary thrombosis, perforated peptic ulcer, and acute pleurisy. Blain, Glynn and Hiratzka state that dissecting aneurysm of the abdominal aorta may, by involving one or both renal arteries, produce a urologic syndrome simulating acute nephrolithiasis or other urinary disorder. Sacks showed electrocardiogram changes *seriatim*, showing the possibility of great diagnostic value in the T-wave changes. Giles reported the case of a patient with a dissecting aneurysm of the femoral artery of undetermined cause, but with unusual symptoms, in which a cure was effected by ligation and a Matas aneurysmorrhaphy. Kinney, Sylvester, and Levine present a report of a case of coarctation of an aorta with a dissecting aneurysm in a 23-year-old pregnant white woman which was diagnosed before death. Henley and Garipey report a case of dissecting aneurysm of the thoracic aorta diagnosed during life and proved at autopsy.

#### SUMMARY

Dissecting aneurysm of the aorta simulates and is often confused with many other disease entities.

There is no single diagnostic guidepost which is conclusive, and there may be broad variations in combinations of signs.

The case of a patient in whom the disease was diagnosed *ante mortem* is reported, together with a detailed anatomical diagnosis by the pathologist.

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## CLINICAL SYMPOSIUM

Prepared under the direction of EDGAR WAYBURN, M.D., *San Francisco*, and  
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### Treatment of Bronchiectasis and Chronic Lung Abscess

#### Medical Aspects:

CLYDE C. GREENE, JR., M.D.

THE term "chronic nontuberculous pulmonary suppuration" is used to denote a group of lung affections of mixed bacterial origin, with anerobic organisms frequently predominating, in which sufficient damage has occurred to the pulmonary parenchyma and bronchial tree to prevent complete and spontaneous resolution. Chronic pulmonary suppuration, regardless of the type, may be manifested clinically by cough, abundant sputum, fever of varying degree, anorexia, malnutrition, weakness, hemoptysis, and recurrent bouts of pneumonitis, but it must be remembered that these diseases are protean in their manifestations and extensive disease can exist without noteworthy clinical evidence of disease.

In this symposium the newer concepts of the pathogenesis and therapy of two types of chronic suppurative pulmonary disease, namely bronchiectasis and lung abscess, will be discussed. These conditions, however, may co-exist to varying degrees in the same area of diseased lung.

#### Bronchiectasis

Both medical and surgical measures are essential in the adequate therapy of bronchiectasis. Perry and King,<sup>9</sup> Alexander,<sup>1</sup> and others agree that about 50 per cent of all patients with bronchiectasis do not have surgical operations. A few in this group should have operations but refuse, while others have so little or so much disease as to contraindicate surgical treatment. The remainder suffer from severe unrelated disease prohibiting operations which otherwise are indicated.

Because of this large group of patients, tremendous interest has been centered on the "nonsurgical" management of the disease. The keynotes of this regimen are drainage, control of infection and the improvement of general health, both mental and physical.

Expulsion of the sputum is best obtained for these patients by postural drainage, which must be a regular part of the life of the medically treated patient and is best carried out from a high bed or table with complete vertical dependence of the trunk. Extreme flexion of the body, as described by Alexander,<sup>1</sup> is also of value when the patient is still able to carry out his normal occupation. Cough depressants reduce the efficacy of postural drainage and

should be avoided, while simple expectorants such as ammonium chloride may be of assistance in promoting drainage.

Control of infection will not produce cure but when properly done will shorten the duration of acute exacerbations and make life more pleasant for the patient. Penicillin, both by inhalation and intramuscular techniques, has assumed a dominant role in the control of infection, but is of principal value when used for short periods to control the acute flare-ups that so regularly appear. In our experience the sulfonamides have been of little value, but success with long continued usage of sulfadiazine in a dosage of 1 gm. daily has been reported.

Other factors in the control of infection and the maintenance of good general health are adequate nutrition, avoidance of severe exposure, change to higher and drier climate (in some cases), and physical and mental adjustment to the disease.

By use of these measures the surgical treatment of bronchiectasis is made more effective and the patient who is not operated upon has an improved prognosis. In fact, Perry and King<sup>9</sup> estimate that 38 per cent of their non-surgical patients now have an excellent working-living capacity.

Thoracic surgeons and internists agree, however, that the best definitive treatment for bronchiectasis is surgical resection of the involved pulmonary tissue. As stated before, this is not feasible in all cases, but today it is possible, with a mortality of less than 5 per cent, to remove all but two of the five usual pulmonary lobes for the complete extirpation of bronchiectatic lung tissue.

The study of Perry and King<sup>9</sup> showed a 12-year mortality of 26 per cent in a group of 4,000 non-surgical patients, with 41 per cent of these deaths occurring within five years after the onset of the disease. Hinshaw and Schmidt<sup>5</sup> have estimated that less than 10 per cent of patients with true bronchiectasis are benefited appreciably by medical treatment alone, and they judge the mortality rate in 15 years after diagnosis to be from 30 to 50 per cent. The younger the patient at onset, the poorer the prognosis without surgical treatment, so that it is particularly important to accurately evaluate bronchiectasis in children and to operate early in all suitable cases. Major thoracic operations are withstood well by children.

Complete visualization of the tracheo-bronchial tree by lipiodol bronchography is essential before resec-

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tion in cases of bronchiectasis. This reveals the degree and extent of pulmonary involvement, and decision as to the amount of pulmonary tissue to be resected must rest solely upon this diagnostic technique. Often the lung tissue appears grossly normal and the extent of the disease cannot be determined by the examining finger so that a preoperative decision as to the amount of tissue to be extirpated must be made.

In this regard several important contributions have been made by Churchill and Belsey,<sup>3</sup> Blades and Kent,<sup>2</sup> and Overholt and Langer.<sup>8</sup> Churchill and Belsey predicated that the essential architectural unit of the lung was not the lobe but the cluster of bronchopulmonary segments comprising a lobe. Each bronchopulmonary segment has now become more or less a surgical unit, and recent efforts at maximum conservation of good pulmonary tissue and function have been directed at segment resections of bronchopulmonary units whenever practical. Successful segmental resection involves detailed knowledge of the anatomy of the pulmonary lobe, but, briefly, it is accomplished by isolating and occluding the involved bronchus, noting the demarkation of the lobule from the remainder of the lobe, dividing the segmental pulmonary vessels, and then stripping the segment from the lobe by dividing the visceral pleura and following normal cleavage planes. Bleeding points on the lung surface are controlled by packs and ligatures.

\* \* \*

### Chronic Abscess of the Lung

Pulmonary abscess, acute and chronic, results from many causes, including aspiration, septic emboli, bronchial obstruction of any type, infection within a pre-existing cyst, or from foreign bodies which enter through the chest wall. Of these, aspiration is by far the most important.

The cause will of course affect the pathologic characteristics of lung abscess, but the majority result from the obstruction of a peripheral bronchus by infected material with destruction and disintegration of the involved bronchopulmonary segment. The abscess, which is usually single, is surrounded by an area of compressed and avascular lung tissue. Usually this causes adjacent pleural adhesions which seal off the pleural space immediately over the abscess, and results in bronchial communication, due to dissolution or dislodgment of the obstruction or to sequestration of necrotic lung tissue.

Signs of chronic abscess of the lung develop within three weeks after the onset of an acute abscess, which is of short duration. The acute phase is the optimal time for both diagnosis and treatment, and it is during this stage that non-surgical methods of treatment have their opportunity for cure. When chronic, a lung abscess is primarily a surgical problem, although here again best results have been obtained by combining adequate medical and surgical treatment.

The fundamental principle in any treatment of lung abscess, regardless of chronicity and the vari-

ability of the clinical manifestations, is adequate drainage. The medical therapy includes drainage, by either postural or bronchoscopic techniques, and drugs. Postural drainage here is of less value than bronchoscopic drainage since the latter permits more complete drainage, the removal of inspissated secretions, the administration of drugs, and, in some instances, the diagnosis of an unsuspected foreign body or neoplasm. Drug therapy today is primarily with penicillin, although in some instances the sulfonamides or streptomycin may prove of value.

If precise localization has been established, conservative treatment of chronic lung abscess is relatively safe because of the peripheral location and the local adherence of the visceral and parietal pleura. Neuhof,<sup>7</sup> in fact, states that the mortality rate of patients with lung abscess treated by early extensive drainage is less than 5 per cent. Samson's<sup>10</sup> concept is that therapy not resulting in both clinical and roentgenological evidence of improvement within two to three weeks should be abandoned. For these reasons external drainage by properly placed rib resection and cavernostomy should be instituted early to prevent irreparable change in the lung.

The advantages of pulmonary resection have been explored, primarily by Sweet,<sup>11</sup> Glover and Clagett,<sup>4</sup> and Lindskog.<sup>6</sup> The present trend is toward the replacement of external drainage by pulmonary resection in chronic abscess, or in any abscess complicated by irreparable lung disease. Glover and Clagett<sup>4</sup> in summation of the general surgical opinion, and as a result of their own experience with 37 cases, list these indications for such pulmonary resection:

1. Persistent symptoms secondary to pathological changes resulting from open drainage.
2. Multiple or multilocular abscesses.
3. Abscesses associated with secondary changes such as fibrosis, bronchiectasis, bronchiostenosis, or atelectasis.
4. Abscesses anatomically located in a position that prohibits drainage.
5. Abscesses in which the diagnosis of malignancy is considered.
6. Abscesses associated from their onset with excessive bleeding.
7. Abscesses in children.
8. Abscesses secondary to foreign bodies not removable by bronchoscopy.

Glover and Clagett report that in 21 cases in which conservative resection was done, there was one death—a mortality rate of 4.8 per cent. In 16 cases in which the lesion was so extensive that pneumonectomy had to be performed, there were six deaths—a mortality rate of 37.5 per cent; but in only seven of these cases, or 44 per cent, were good results obtained.

Future treatment of chronic lung abscess should be directed toward prevention, by means of prompt and adequate medical treatment or by early adequate external drainage, and resection, rather than dependence on repeated external drainages, plastic procedures, or thoracoplasty. The necessity for resection should be recognized and accepted and in many of

the "early" chronic cases, particularly if there is associated pulmonary disease, resection should take precedence over external drainage as the initial procedure.

\* \* \*

To conclude, it may be said that the following developments made during the past 15 years have entirely altered the management and prognosis of the patient with chronic nontuberculous pulmonary disease:

1. Improvements in the diagnostic techniques, namely roentgenology and bronchoscopy.

2. Improvements in the control of infection by chemotherapeutic agents, namely penicillin, streptomycin and the sulfonamides.

3. Improvements in the control of shock from blood loss, permitting longer and more extensive surgical operation.

4. Improvements in the technique of intratracheal positive pressure anesthesia by which cardiorespiratory embarrassment incident to an open pneumothorax can be prevented.

5. Improvements in the technique of closure of a divided bronchus, preventing bronchial fistulae.

6. Improvements in the individual ligation technique in the management of major pulmonary vessels, preventing secondary hemorrhages.

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## MEDICAL PROGRESS:

# Isotopes in Clinical and Experimental Medicine\*

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*This is Part I of an article in two parts. Part II, Important Applications of Isotopes in Experimental Medicine, will appear in the August issue.*

### INTRODUCTION

IN 1898—now 50 years ago—the Curies discovered radium ( $_{88}\text{Ra}$ ). Their announcement, following only two years after Becquerel's discovery of the natural radioactivity associated with uranium ( $_{92}\text{U}$ ) salts, not only presaged a vast new era in physics, but also in medicine. Within a few years after the existence of radium was announced, it had come into use in clinical practice—in the treatment of certain malignancies and dermatoses. These uses of radium are examples of the application of isotopes to medical problems. The 50 years since the Curies' demonstration of the existence of radium have witnessed many advances in medicine as a result of such application.

The concept of the "isotope" did not develop, however, until work on the natural radioactive series—of uranium and thorium ( $_{90}\text{Th}$ ) parentage—had been under way for several years. It was early recognized that the spontaneous decay of the heaviest elements behaved according to a regular pattern. During the first decade of the 20th century "elements" were discovered that had quite different decay characteristics, but were chemically identical. Thus radium and mesothorium 1 ( $\text{MsTh}_1$ ) were found to be chemically inseparable, but to have quite different decay patterns—the former (as is now known) giving off alpha and gamma rays with a half-life of about 1590 years; the later, beta rays with a half-life of 6.7 years. The English physicist, Soddy, fitted these facts together and recognized that, at least among the heaviest elements, there could be two or more forms of a given element differing by nuclear mass. For these different forms of a single element he coined the name *isotope*.

The earliest isotopes were distinguished by their different radioactive properties, and all belonged to the three natural radioactive series of heaviest elements. But Soddy suspected that stable elements also might consist of mixtures of more than one nuclear form. He and his associates studied lead ( $_{82}\text{Pb}$ ) from different sources; this element was known to be the end product of the natural radioactive series.

They demonstrated quite clearly that lead in thorium ore was lighter than lead from other sources. By 1920 the existence of more than one nuclear form of a light element unrelated to the natural radioactive series was conclusively shown by the work of Aston with neon ( $_{10}\text{Ne}$ ).

Today we know that all of the 96 elements so far discovered may exist in more than one nuclear form. Of the 81 stable elements 60 exist as more than one stable isotope. There are in addition over 600 known unstable species—at least one such isotope being known for each of the 96 elements. Only a small proportion of these exist in nature in detectable form. The others are *artificial* radioisotopes made in the laboratory principally by the cyclotron and nuclear pile reactor; all of these have been found since the discovery of artificial radioactivity by the Joliot-Curies in 1933.

The use of isotopes in medicine depends upon the exploitation of certain of their nuclear properties. For example, the radiations accompanying the decay of a few unstable isotopes have made possible their use in therapy. At the present time, radium is the best known example of an isotope of importance in radiotherapy. Strictly speaking, however, what we commonly call "radium" is only one isotope of the element  $_{88}\text{Ra}$ —the one characterized by a nucleus of 226 mass units and a long half-life (1590 years). In addition to  $_{88}\text{Ra}^{226}$  there are also known the species  $_{88}\text{Ra}^{223}$  ( $\text{AcX}$ ),  $_{88}\text{Ra}^{224}$  ( $\text{ThX}$ ), and  $_{88}\text{Ra}^{228}$  ( $\text{MsTh}_1$ ) with half-lives of 11.2 days, 3.64 days, and 6.7 years respectively.

Much more important than the direct use of radioisotopes in therapy, however, is the application of isotopes as *tracers* in the study of living processes. It is possible to employ both stable and radioactive species in this manner. Artificial radioisotopes can be introduced into biological systems and their fate studied by following the distribution of the decaying atoms. Stable isotopes separated from their more abundant homologues or enriched in relation to these can also be introduced into biological systems and followed by studying the fluctuations in isotope ratios. With such tracers it has been possible to study many metabolic processes formerly unapproachable, even indirectly. The store of new knowledge made available with isotopes is already great, but the potentialities of these applications have been little more than touched.

The isotopes that have been used in fundamental investigations in medicine and related fields are listed with their principal applications in the accompanying Table 1. It is to be noted that only seven

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\*The preparation of this paper was aided in part by the Henry Stephens Kiersted Memorial Fund for Medical Research.



stable isotopes have so far found biological use. However, this list of stable species will unquestionably be somewhat expanded in the near future since the United States Atomic Energy Commission<sup>144</sup> has recently announced the availability in limited quantities of a number of additional separated isotopes. Most of the rare species of value in tracer work are heavier than the most abundant species of the same elements; hence the stable tracers are commonly referred to as "heavy isotopes." Altogether there are 278 known stable isotopes belonging to 81 elements; 197 of these are less abundant species of the 60 elements existing in more than one stable form. A good number of these will quite probably find biological application. From the accompanying table it may also be seen that over 70 radioisotopes have found biological application. Of the more than 600 known radioactive isotopes, about 160 have properties that adapt them to biological tracer work. Thus not quite half of the potentially valuable unstable species have so far been applied biologically. However, many of those remaining will doubtless be employed in the near future in tracer experiments. The availability of a large number of radioisotopes has been announced by the United States Atomic Energy Commission.<sup>145</sup>

Some of the important studies with isotopes are dealt with in the remaining part of this paper. It is not intended that our coverage be comprehensive. Aside from the role of radioisotopes in therapy the discussion will center around their use as tools for the elucidation of physiological processes. A truly comprehensive survey of tracer applications would cut across all the experimental fields of biology and inevitably separate in a somewhat artificial manner isotopic from non-isotopic studies of the same phenomena. However, tracer research is one of the most important aspects of modern experimental science, particularly biology (and therefore medicine); a survey of some of the more important achievements with isotopes is thus, we believe, of interest. It is hoped that the reader will thereby gain orientation in this rapidly growing and vital field. For reasons of limitation in space we are not dealing here with the theory and techniques of isotope production, use, and measurement. For detailed treatment of this subject in relation to radioisotopes we refer the reader to the recent book by Kamen<sup>70</sup> and that edited by Lawrence and Hamilton.<sup>80</sup> As yet, however, no detailed treatment of stable isotopes in biology exists in book form.

Of the two sections that comprise the remainder of this paper, the first deals with the clinical application of isotopes and the second with their application to problems in experimental medicine.

#### CLINICAL APPLICATIONS OF ISOTOPES

##### *General Considerations:*

Radium and radon ( $^{86}\text{Rn}$ ), and their decay products, have been used for over 45 years in the treatment of various malignancies and dermatoses. These

applications are familiar to the medical profession as a whole and need not be detailed here.

As indicated in Table 1 artificial isotopes of two elements, phosphorus ( $^{32}\text{P}$ ) and iodine ( $^{131}\text{I}$ ), have thus far been employed in therapy with definite success. Others—sodium ( $^{22}\text{Na}$ ), manganese ( $^{55}\text{Mn}$ ), zinc ( $^{65}\text{Zn}$ ), strontium ( $^{90}\text{Sr}$ ), yttrium ( $^{90}\text{Y}$ ), zirconium ( $^{90}\text{Zr}$ ), columbium ( $^{94}\text{Nb}$ ), and gold ( $^{198}\text{Au}$ )—have received preliminary trial, but therapeutic techniques with these elements are still in the experimental stage. A number of isotopes have also been employed for diagnostic purposes. These are discussed in the following subsections.

The isotopes that so far have shown definite value in therapy and diagnosis have been those that demonstrate a fair degree of selective localization, as the result either of their normal fate in metabolism or of their fate as special compounds or colloids. Thus  $^{32}\text{P}$  concentrates to some degree in rapidly growing tissue (particularly in the nucleoprotein fraction) and in bone;  $^{131}\text{I}$  localizes in the thyroid gland (at least several hundred times the concentration in the rest of the body); and certain colloidal preparations can be made that localize in various parts of the reticuloendothelium or at the point of injection.

So far, all therapeutic techniques of radiation with isotopes, except for the treatment of hyperthyroidism with radioiodine, have suffered from the limited selectivity of uptake by the diseased tissue over normal tissues. For example, in the treatment of diseases of the bone marrow and lymphatic system with radioactive  $^{32}\text{P}$  it is impossible to avoid to a greater or lesser extent the irradiation in various parts of the body of those normal cells that metabolize rapidly and others in their immediate vicinity. Actually, in the treatment of polycythemia vera, for example, it would be desirable if irradiation could be delivered only to the nucleated red cells; and in lymphosarcoma and leukemia only to the offending leukocytes or lymphosarcoma cells, and not to the normal cells, especially the platelet and red cell producing centers. Some additional progress may be anticipated in the management of these blood dyscrasias by the application of labeled colloids. The work of Jones, Wrobel, and Lyons<sup>68</sup>, and the more recent work of Dobson *et al.*<sup>23</sup>, shows that radiation may be limited largely to the liver and spleen by the use of anhydrous colloidal chromic phosphate labeled with  $^{32}\text{P}$ , which localizes selectively in the reticuloendothelial cells of the liver and spleen when introduced intravascularly in a highly dispersed form. Similar properties have been found by Dobson *et al.*<sup>22</sup> for a number of other colloids—of  $^{90}\text{Y}$ ,  $^{90}\text{Zr}$ , and  $^{94}\text{Nb}$ —which may be labeled with radioisotopes of these respective elements. Some of the colloids can be concentrated to a high degree in the bone marrow, others in the liver and spleen. Other colloids suggested are those of  $^{55}\text{Mn}$  (Hahn and Sheppard<sup>48</sup>; and Sheppard and Hahn<sup>126</sup>).

However, for neoplastic diseases in general, localizing substances of adequate selectivity that can be labeled and used for radiotherapy have not been

TABLE 1.—Important Stable and Radioactive Isotopes That Have Been Used in Basic Medical and Related Investigations†

*Element	‡Isotope		Some problems in which isotope has been used
	Stable	Radioactive	
*Hydrogen ( ${}_1\text{H}$ )	${}_1\text{H}^1$		High speed proton irradiation (suggested) 150
	* ${}_1\text{H}^2$ (D)		Intermediary metabolism, 70, 122; body water turnover, 61-63; and content, 63, 99
		${}_1\text{H}^3$ (T)	Body water content, 107; photosynthesis, 70
Lithium ( ${}_3\text{Li}$ )	${}_3\text{Li}^6$ (in natural element)		Slow neutron therapy of experimental tumors, 73, 153
Beryllium ( ${}_4\text{Be}$ )		${}_4\text{Be}^7$	Absorption, distribution, and excretion, 51
	${}_4\text{Be}^9$ (in natural element)		Fast neutron irradiation and therapy, 1, 132
Boron ( ${}_5\text{B}$ )	${}_5\text{B}^{10}$ (in natural element)		Slow neutron therapy of experimental tumors, 153
		${}_5\text{B}^{11}$	Intermediary metabolism, 12, 119, 150, 151; CO distribution and elimination, 141; photosynthesis, 120
*Carbon ( ${}_6\text{C}$ )	* ${}_6\text{C}^{13}$		Intermediary metabolism, 12, 145, 150, 151
		${}_6\text{C}^{14}$	Photosynthesis, 6; other preliminary tracer work, 8
*Nitrogen ( ${}_7\text{N}$ )		${}_7\text{N}^{13}$	Respiratory gas exchange, 66; supposed nitrogen fixation by barley, 118
	* ${}_7\text{N}^{15}$		Intermediary metabolism, 145
*Oxygen ( ${}_8\text{O}$ )	* ${}_8\text{O}^{18}$		Photosynthesis, 121; bacterial fractionation, 24
Fluorine ( ${}_9\text{F}$ )		${}_9\text{F}^{18}$	Bone and tooth physiology and chemistry, 147
*Sodium ( ${}_{11}\text{Na}$ )		${}_{11}\text{Na}^{22}$	Retention in congestive heart disease, 112; effect of dietary chloride deficiency, 19
		${}_{11}\text{Na}^{24}$	Electrolyte metabolism, 33, 34, 43, 45, 49, 54, 69, 92, 146; adrenal physiology, 3-5; therapy of leukemia, 85, 139
		${}_{12}\text{Mg}^{27}$	Photosynthesis, 117
*Magnesium ( ${}_{12}\text{Mg}$ )			Mineral metabolism, 15, 16, 60; intermediary metabolism, 13, 41a, 59; therapy of chronic leukemias, polycythemia vera, etc., 29, 30, 65, 74-79, 82, 115, 148, and skin lesions, 88, 90; labeling of erythrocytes, 103; diagnosis of malignancy, 89, 91; colloids localizing in the reticuloendothelial system, 2, 22, 23, 67
*Phosphorus ( ${}_{15}\text{P}$ )		${}_{15}\text{P}^{32}$	Intermediary metabolism, 26
*Sulfur ( ${}_{16}\text{S}$ )	* ${}_{16}\text{S}^{34}$		Intermediary metabolism, 95, 96, 134-137; thiamine metabolism, 10; mineral metabolism, 27, 129
		${}_{16}\text{S}^{35}$	

Element	Radioactive Isotope	Some problems in which isotope has been used
*Chlorine ( ${}_{17}\text{Cl}$ )	${}_{17}\text{Cl}^{38}$	Mineral metabolism, 45, 93
Argon ( ${}_{18}\text{Ar}$ )	${}_{18}\text{Ar}^{41}$	Respiratory gas exchange; blood circulatory pattern, 66
*Potassium ( ${}_{19}\text{K}$ )	${}_{19}\text{K}^{42}$	Mineral metabolism, 32, 43, 45, 105; adrenal physiology, 3-5
*Calcium ( ${}_{20}\text{Ca}$ )	${}_{20}\text{Ca}^{41}$ ${}_{20}\text{Ca}^{45}$	Mineral metabolism, 42
*Manganese ( ${}_{25}\text{Mn}$ )	${}_{25}\text{Mn}^{52}$ ${}_{25}\text{Mn}^{54}$	Distribution of colloidal $\text{MnO}_2$ in reticuloendothelial system, 48, 126
	${}_{25}\text{Mn}^{52}$ ${}_{25}\text{Mn}^{54}$	Mineral metabolism, 44
	${}_{25}\text{Mn}^{56}$	Mineral metabolism, 9
	${}_{26}\text{Fe}^{55}$ ${}_{26}\text{Fe}^{59}$	Mineral metabolism, 46, 47, 98; blood physiology, 37-39; and preservation, 35, 36, 116

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Element	Radioactive Isotope	Some problems in which isotope has been used
? *Cobalt ( $_{27}\text{Co}$ )	$_{27}\text{Co}^{58}$ ( $_{27}\text{Co}^{57}$ ) $_{27}\text{Co}^{58}$	Mineral metabolism, 44
*Copper ( $_{29}\text{Cu}$ )	$_{29}\text{Cu}^{64}$	Mineral metabolism, 152
? *Zinc ( $_{30}\text{Zn}$ )	$_{30}\text{Zn}^{63}$ $_{30}\text{Zn}^{65}$	Interstitial injection of pectin-protected colloid, 102 Mineral metabolism, 125
Arsenic ( $_{33}\text{As}$ )	$_{33}\text{As}^{74}$	Absorption, distribution, and excretion, 25, 64; experimental filariasis, 83
Selenium ( $_{34}\text{Se}$ )	$_{34}\text{Se}^{83}$	Absorption, distribution, and excretion, 94
? *Bromine ( $_{35}\text{Br}$ )	$_{35}\text{Br}^{82}$	Electrolyte exchange, 43, 45; thyroid physiology, 109; distribution of brominated dyes, 100
Krypton ( $_{36}\text{Kr}$ )	$_{36}\text{Kr}^{79, 81}$	Respiratory gas exchange; blood circulatory pattern, 66, 140
Rubidium ( $_{37}\text{Rb}$ )	$_{37}\text{Rb}^{86}$	Electrolyte exchange, 43
Strontium ( $_{38}\text{Sr}$ )	$_{38}\text{Sr}^{85}$	Absorption, distribution, and excretion, 51
	$_{38}\text{Sr}^{89}$	Bone physiology, 42, 50, 108
	$_{38}\text{Sr}^{90}$	Absorption, distribution, and excretion, 50
	$_{38}\text{Y}^{88}$	Absorption, distribution, and excretion, 50
Yttrium ( $_{39}\text{Y}$ )	$_{39}\text{Y}^{91}$	Absorption, distribution, and excretion, 50; colloids in reticuloendothelial system, 22, 23
	$_{40}\text{Zr}^{90}$	Absorption, distribution, and excretion, 51
Zirconium ( $_{40}\text{Zr}$ )	$_{40}\text{Zr}^{95}$	Absorption, distribution, and excretion, 50; colloids localizing in reticuloendothelial system, 22, 23
	$_{41}\text{Nb}^{95}$	Absorption, distribution, and excretion, 50; colloids localizing in reticuloendothelial system, 22
Columbium ( $_{41}\text{Cb}$ )	$_{41}\text{Nb}^{95}$	Absorption, distribution, and excretion, 50; colloids localizing in reticuloendothelial system, 22
Molybdenum ( $_{42}\text{Mo}$ )	$_{42}\text{Mo}^{99}$	Absorption, distribution, and excretion, 104
Ruthenium ( $_{44}\text{Ru}$ )	$_{44}\text{Ru}^{103}$ $_{44}\text{Ru}^{106}$	Absorption, distribution, and excretion, 50
Antimony ( $_{51}\text{Sb}$ )	$_{51}\text{Sb}^{124}$	Absorption, distribution, and excretion; experimental filariasis, 11
Tellurium ( $_{52}\text{Te}$ )	$_{52}\text{Te}^{121}$	Absorption, distribution, and excretion, 20
	$_{52}\text{Te}^{127}$ $_{52}\text{Te}^{129}$	Absorption, distribution, and excretion, 50
	$_{53}\text{I}^{128}$	Iodine metabolism and thyroid physiology, 84
	$_{53}\text{I}^{130}$ $_{53}\text{I}^{131}$	Iodine metabolism and thyroid physiology, 57, 84, 138; therapy of thyrotoxicosis, 14, 52, 56, 58; and metastatic thyroid carcinoma, 123, 124; absorption of insulin, 114
*Iodine ( $_{53}\text{I}$ )	$_{53}\text{I}^{130}$ $_{53}\text{I}^{131}$	Respiratory gas exchange; blood circulatory pattern, 66; narcotic effects, 81
Xenon ( $_{54}\text{Xe}$ )	$_{54}\text{Xe}^{127}$	Absorption and distribution, 50
	$_{54}\text{Xe}^{133}$	Absorption, distribution, and excretion, 51
Cesium ( $_{55}\text{Cs}$ )	$_{55}\text{Cs}^{134}$	Absorption, distribution, and excretion, 50
	$_{55}\text{Cs}^{135}$	Absorption, distribution, and excretion, 51
Barium ( $_{56}\text{Ba}$ )	$_{56}\text{Ba}^{133}$	Absorption, distribution, and excretion, 50
	$_{56}\text{Ba}^{140}$	Absorption, distribution, and excretion, 50
Lanthanum ( $_{57}\text{La}$ )	$_{57}\text{La}^{140}$	Absorption, distribution, and excretion, 50
Cerium ( $_{58}\text{Ce}$ )	$_{58}\text{Ce}^{141}$	Absorption, distribution, and excretion, 50
	$_{58}\text{Ce}^{144}$	Absorption, distribution, and excretion, 50
Praseodymium ( $_{59}\text{Pr}$ )	$_{59}\text{Pr}^{142}$	Absorption, distribution, and excretion, 50

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Element	Radioactive Isotope	Some problems in which isotope has been used
Element 61	$^{61}_{147}$	Absorption, distribution, and excretion, 50
Gold ( $^{79}_{198}\text{Au}$ )	$^{79}_{198}\text{Au}$	Absorption, distribution, and excretion, 28; chrysotherapy in arthritis, 7; colloidal therapy, 46a, 125a
Mercury ( $^{80}_{197}\text{Hg}$ )	$^{80}_{197}\text{Hg}$	Mercury vapor as an industrial health hazard, 40
Lead ( $^{82}_{210}\text{Pb}$ )	$^{82}_{210}\text{Pb}$ (RaD)	Absorption, distribution, and excretion, 17, 101
	$^{82}_{212}\text{Pb}$ (ThB)	Absorption, distribution, and excretion, 21
Bismuth ( $^{83}_{210}\text{Bi}$ )	$^{83}_{210}\text{Bi}$ (RaE)	Absorption, distribution, and excretion, 72
Astatine ( $^{85}_{211}\text{At}$ )	$^{85}_{211}\text{At}$	Thyroid physiology, 53
Radon ( $^{86}_{220}\text{Rn}$ )	$^{86}_{220}\text{Rn}$ (Tn)	Elimination in breath, 130
	$^{86}_{222}\text{Rn}$	Numerous studies on uptake and elimination in breath, distribution, etc.; treatment of various malignancies and dermatoses
Radium ( $^{88}_{226}\text{Ra}$ )	$^{88}_{226}\text{Ra}$	Numerous studies on distribution, toxicity, etc.; treatment of various malignancies and dermatoses
	$^{88}_{228}\text{Ra}$ (MsTh <sub>1</sub> )	
	$^{90}_{228}\text{Th}$ (RdTh)	Absorption, distribution, and excretion, 50
Thorium ( $^{90}_{232}\text{Th}$ )	$^{90}_{232}\text{Th}$ (natural element)	Numerous studies on distribution, toxicity, etc.
	$^{90}_{234}\text{Th}$ (UX <sub>1</sub> )	Absorption, distribution, and excretion, 50
	$^{91}_{233}\text{Pa}$	Absorption, distribution, and excretion, 50
Protoactinium ( $^{91}_{233}\text{Pa}$ )	Natural element	Numerous studies on distribution, toxicity, etc.
Uranium ( $^{92}_{235}\text{U}$ )	$^{92}_{235}\text{U}$ (AcU)	Production of slow neutrons, 128; effect of fission from colloids localizing in reticuloendothelial system, 142
Neptunium ( $^{93}_{237}\text{Np}$ )	$^{93}_{237}\text{Np}$	Absorption, distribution, and excretion, 50
Plutonium ( $^{94}_{239}\text{Pu}$ )	$^{94}_{239}\text{Pu}$	Absorption, distribution, and excretion, 50
Americium ( $^{95}_{241}\text{Am}$ )	$^{95}_{241}\text{Am}$	Absorption, distribution, and excretion, 50
Curium ( $^{96}_{242}\text{Cm}$ )	$^{96}_{242}\text{Cm}$	Absorption, distribution, and excretion, 50

<sup>1</sup>See also the book by Govaerts (1945)<sup>41</sup> on the use of stable isotopes and the recent book by Kamen (1947)<sup>70</sup> and Lawrence and Hamilton (1948)<sup>90</sup> on the use of radioisotopes in biology.

\*Elements known or believed to be essential in mammalian nutrition based on the book by Shohl (1939)<sup>127</sup>; those for which unanimity is lacking are also marked with a question mark (?).

†An isotope is placed in parentheses if it occurs together with another isotope (of the same element) used for tracer work, but is itself not significant for the tracer purposes to which the mixture may be applied. Two or more isotopes are connected by a brace if they occur together in tracer preparations and are of about equal importance.

found. If such are found, it would be desirable that they carry a radioactive isotope which emits a very soft ray, such as radiohydrogen ( $^1_1\text{H}^3$ ) or long-lived radiocarbon ( $^{12}_6\text{C}^{14}$ ). Even these emit beta-rays that traverse several cell diameters; however, the half-penetration of the  $^1_1\text{H}^3$  beta-ray is less than the radius of the average cell.

#### *Radiophosphorus ( $^{32}_{15}\text{P}$ ) in Therapy and Diagnosis:*

The first radioisotope to be used in therapy was  $^{32}_{15}\text{P}$ . It was employed as early as 1936 by Lawrence and associates<sup>74</sup> in the treatment of chronic leukemia and polycythemia vera. In the treatment of chronic leukemia, results with this isotope are good, and in the treatment of polycythemia vera, excellent, as brought out in the studies of a large group of patients treated since 1936<sup>75-79, 82</sup>. Other workers have later taken up similar studies, and there are reports by Reinhard *et al.*<sup>115</sup>, Erf<sup>29, 30</sup>, Warren<sup>148</sup>, Jacobson *et al.*<sup>65</sup>, and others.  $^{32}_{15}\text{P}$  in soluble form (in labeled isotonic  $\text{Na}_2\text{HPO}_4$ ) given by mouth or vein is used in

the treatment of these blood dyscrasias. The determination and calculation of dosage, routes of administration, and supportive treatment of patients receiving this type of therapy are discussed in most of the works cited.

It is at the present time the treatment of choice for many cases of polycythemia (rubra) vera (i.e., primary polycythemia, erythremia, or Osler-Vaquez's disease). In most patients complete hematological remission and almost complete symptomatic relief can be effected. A single course of treatment may bring about a remission lasting many years. A recent analysis of end results in a series of 100 patients with polycythemia vera, and treated with  $^{32}_{15}\text{P}$ <sup>76-78</sup>, is very encouraging. The average age at onset of the disease in the group was 48. Administration of  $^{32}_{15}\text{P}$  was necessary on the average of one course every three years, in order to keep the red cells at normal or near normal levels and for the relief of symptoms. In the group of 15 patients who have died from various causes, the average age at death was 67—



## L. J. POLYCYTHEMIA VERA (Age 32, Female)

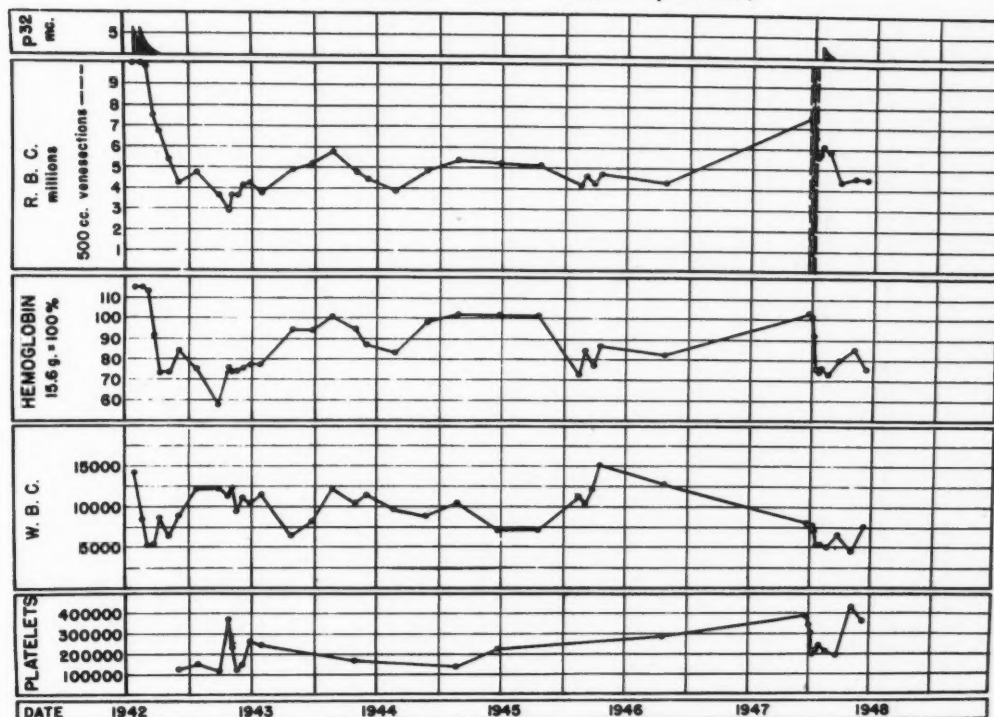


Figure 1.—This patient with classical polycythemia vera with enlarged spleen received 2 doses of  $P^{32}$  in 1942, resulting in a remission lasting over 5 years. Retreatment in 1948 has brought about another remission which continues.

giving these people a near normal life expectancy. It is of interest to point out that insulin is considered a control for diabetes, yet life expectancy in a recent large series reported by Lombard and Joslin<sup>87</sup> was only 10 years. Figures 1 and 2 are representative charts showing the hematological response to treatment.

For the treatment of chronic leukemia, both lymphatic and myelogenous,  $^{15}P^{32}$  is at least as satisfactory in producing hematological and symptomatic remissions as x-ray and it now appears that it prolongs life somewhat longer<sup>77, 79, 82</sup>. There is another definite advantage of it over x-ray, namely, that the former practically never produces radiation sickness. In a series of over 300 patients with chronic leukemia, treated with  $^{15}P^{32}$ —beginning in 1936—the average duration of life after onset is approaching five years and this life duration is largely comfortable and useful. In this series over 30 per cent of the patients have lived over five years and some much longer. Figures 3, 4, and 5 are representative charts. Figure 6 is the chart of a young man suffering from polycythemia vera complicated by a leukemic blood picture. It is to be noted that the leukemic picture has been cleared up with  $P^{32}$ .

In none of these serious diseases has there been subsequently observed the induction of other tumors

as a result of radiophosphorus therapy; yet several hundred patients have been treated and observed since 1936.

Complications of soluble  $^{15}P^{32}$  therapy are leukopenia, thrombocytopenia, and anemia, and these constitute limiting factors in the dosage. In a few cases x-radiation has value in conjunction with  $^{15}P^{32}$  therapy in reducing more rapidly the size of lymph nodes in lymphatic leukemia and in combating splenomegaly, particularly in myeloid leukemia. It has been common experience among workers concerned that therapy with  $^{15}P^{32}$  requires a considerable degree of individualization. Its limitations in the form of the soluble phosphate for blood diseases are brought out in a recent article by Graff, Scott and Lawrence<sup>41a</sup>.

$^{15}P^{32}$  in the treatment of skin lesions has been described by Low-Beer<sup>88, 90</sup>. He soaks a small piece of blotting paper in a labeled phosphate solution and applies this to the surface of the tumor or other skin lesion. The beta-rays from  $^{15}P^{32}$  have a "half-penetration" of about 1 mm. in tissue, and this suggests  $^{15}P^{32}$  may prove superior to x-ray or  $^{88}Ra$  in the treatment of certain radiosensitive superficial skin lesions by avoiding irradiation of the deeper, uninvolved tissues.

## V.B. POLYCYTHEMIA VERA (Age 53, Male)

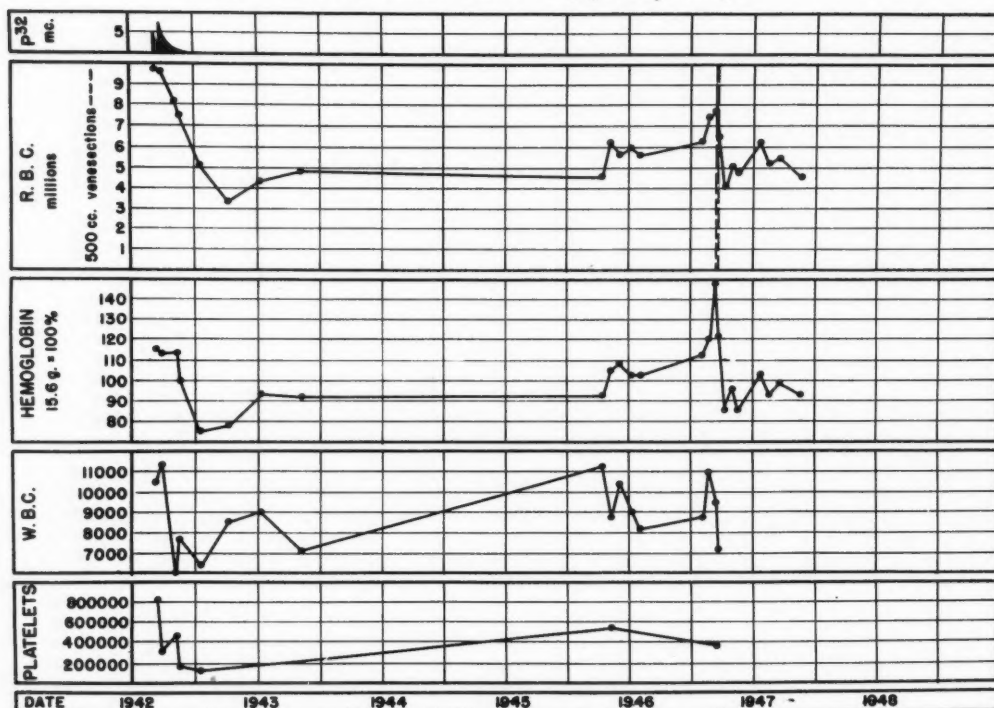


Figure 2.—Two injections of approximately 5 mc P<sub>32</sub> in 1942 brought about hematological and clinical remission. In 1947, a moderate rise in the red cell level has been controlled by two venesections.

<sup>15</sup>P<sup>32</sup> has also been used for experimental therapeutic purposes, in an insoluble colloid anhydrous chronic phosphate. Exploratory work during the past few years on the therapy of the splenomegaly and hepatomegaly of chronic leukemia and other diseases with this material has been carried on.<sup>67</sup> Another possible application of labeled chronic phosphate and colloids with similar properties is their use in the interstitial infiltration of chemically inert radioactive material into malignant growths. Allen *et al*<sup>2</sup> have injected chronic phosphate into the tissues around transplanted mouse tumors. They showed that the colloid remains at the point of injection and that the radioactive material can cause regression of mammary tumors under a certain size. Clinically this technique has recently been used for the injection of enlarged superficial lymph nodes in leukemia (Jones *et al*.<sup>67</sup>). It is possible that a similar procedure may prove of some value in the treatment of malignancies in inoperable sites.

The use of <sup>15</sup>P<sup>32</sup> as a possible diagnostic tool has been suggested by Low-Beer and associates<sup>89, 91</sup>. They have found in a few cases that, if small doses of labeled Na<sub>2</sub>HPO<sub>4</sub> are given to women with suspected breast carcinoma, the activity of the superficially located, malignant lesion (except for slowly growing mucoid carcinomata) is 25 per cent or more

above that of the surrounding tissue of the skin. Benign lesions in their series showed less than 25 per cent greater activity. For such work the Strajman counter, a small mica-window Geiger-Müller counter that can measure gamma-rays and energetic beta-rays from *in vivo* sources (Strajman<sup>133</sup>), should have considerable value, particularly if localizing compounds emitting gamma-rays can be found.

<sup>15</sup>P<sup>32</sup> has thus been shown to have considerable therapeutic value. Further research may well expand its clinical usefulness in the form of other inorganic or organic compounds, both in therapy and diagnosis.

#### Radioiodine (<sup>53</sup>I<sup>130</sup> and <sup>53</sup>I<sup>131</sup>) in Therapy and Diagnosis:

The therapeutic use of radioactive iodine was reported upon for the first time simultaneously in 1942 by the Boston group<sup>56</sup> and the California group<sup>52</sup>, for the treatment of hyperthyroidism (i.e., thyrotoxicosis, Grave's disease, Basedow's disease, etc.). Comprehensive reports on two series of patients with hyperthyroidism appeared in 1946, one by the former authors (Hertz and Roberts<sup>58</sup>) and the other by Chapman and Evans<sup>14</sup>.

For therapeutic purposes carrier-free radioiodine in the form of an aqueous NaI solution is used, being administered by mouth. In the two most recent

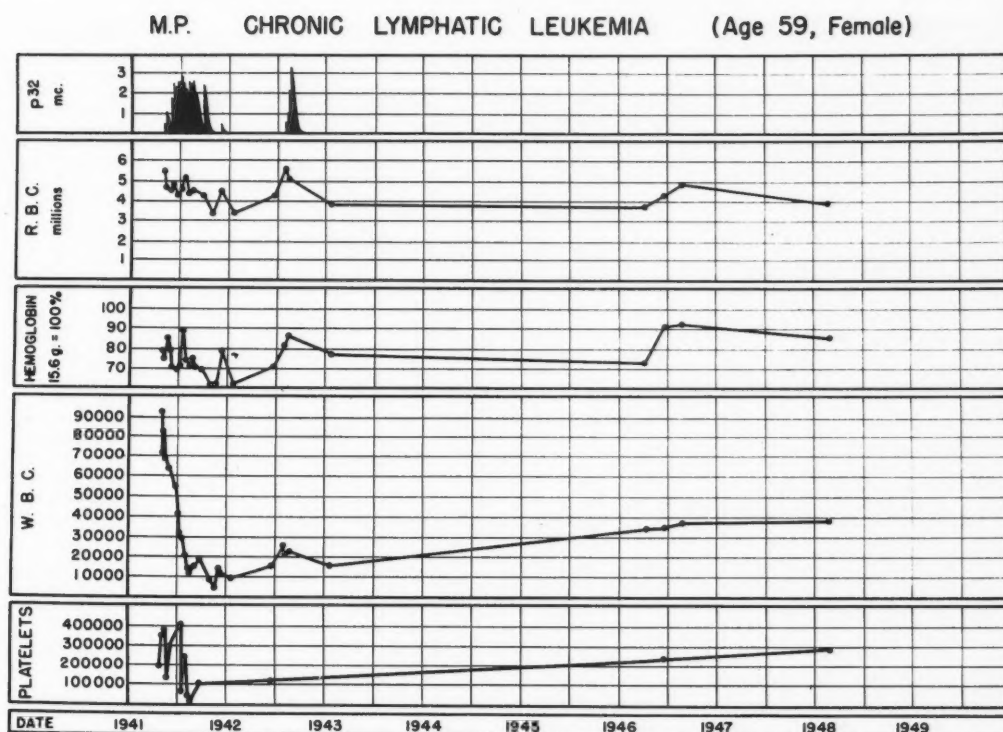


Figure 3.—Chronic lymphatic leukemia treated with multiple small doses of  $P_{32}$  in 1941 and 1942. There has been no treatment since then and the remission has lasted over six years.

papers, the iodine has consisted of a mixture of  $^{53}I^{130}$  and  $^{53}I^{131}$ , of which the former has been the clinically more important component. The determination and calculation of dosage are given both by Hertz and Roberts and by Chapman and Evans.

Hertz and Roberts have found that about 80 per cent of their patients having thyroids of 60-75 gm. in size, and treated with an appropriate dose of radioiodine have been effectively cured. Chapman and Evans have also reported encouraging results. A complication of this form of therapy has been myxedema, resulting from an excessive depression of thyroid function, but as yet there have been no other post-irradiation effects such as the induction of carcinoma. The ultimate evaluation of this form of therapy as compared with other methods must await more extensive work and the passage of time.

In the last few years workers have also reported a few cases in which treatment of iodine-metabolizing thyroid malignancy has met with partial or considerable success when radioiodine has been used. Seidlin *et al.*<sup>123, 124</sup> have recently reported in detail on a case of metastatic thyroid adenocarcinoma in which metastases took up iodine. This patient responded favorably to radioiodine therapy administered on three occasions—in March, 1943, April, 1944, and March, 1945. It would, therefore, appear

that such treatment can be of value for those thyroid malignancies in which iodine is concentrated.

As a diagnostic tool for the determination of the level of the thyroid function, radioiodine appears to offer good clinical possibilities. So far most of the publications dealing with thyroid physiology as studied with radioiodine have been in the nature of fundamental investigations rather than of diagnostic developments. Hertz and Roberts<sup>57</sup>, however, have shown that radioiodine can be used in distinguishing between simple hyperthyroidism and the ophthalmopathic type.

In general the use of radioiodine for the treatment and diagnosis of certain thyroid diseases appears highly promising.

#### Other Isotopes in Therapy and Diagnosis:

The use of isotopes of  $^{11}Na$  and  $^{38}Sr$  in therapy has been reported by various workers in the last few years. In addition, recent work with phosphate,  $^{25}Mn$ ,  $^{30}Zn$ ,  $^{39}Y$ ,  $^{40}Zr$ ,  $^{41}Cb$ , and  $^{79}Au$  colloids shows promise.

Radiosodium  $^{11}Na^{24}$  as labeled  $NaCl$  has been applied in the treatment of chronic leukemia by Thygesen, Vidaback, and Villaume<sup>139</sup> and by Lindgren<sup>85</sup>. The former workers observed favorable results in 7 cases of chronic lymphatic leukemia, but the report extended only over a period of 150 days. Lindgren.

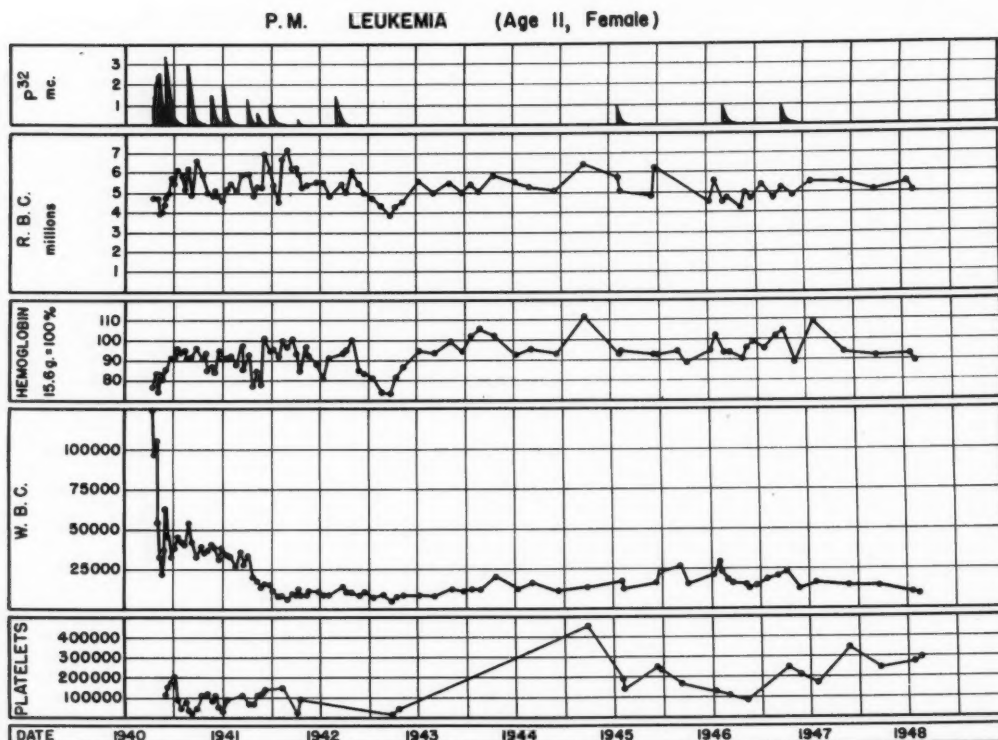


Figure 4.—Chronic myelogenous leukemia in a young girl treated in 1940, 1941, 1942, and in 1945 and 1946. The disease has been easy to control.

who treated five cases of leukemia with radiosodium and radiophosphorus, found that  $^{32}\text{P}$  gave a much better response. A more recent paper by Evans and Quimby<sup>31</sup> on the effect of  $^{24}\text{Na}$  on normal and leukemic mice suggests that this form of therapy may prove comparable to total body roentgen radiation. These workers found that the hematological response in normal animals was roughly the same with  $^{24}\text{Na}$  as with equivalent roentgen irradiation. They did not, however, compare roentgen irradiation with  $^{24}\text{Na}$  therapy in their leukemic animals, which appeared after administration of  $^{24}\text{Na}$  to show a more rapid, although less prolonged, fall in the leukocyte count than did the normal. There are as yet insufficient published data for an evaluation of radiosodium therapy in chronic leukemia, but it is expected that the results would be similar to those following total body irradiation with x-rays, since there is for all practical purposes no selective localization of sodium.

The usefulness of  $^{24}\text{Na}$  as a diagnostic tool is evident from a recent review by Quimby<sup>11</sup>. She has reported that in a number of circulatory diseases (arteriosclerosis, Raynaud's disease, etc.) and injuries (trench- and immersion-foot, frost-bite, etc.) of the extremities it has proved of considerable value in determining the status of the circulation. Since  $^{24}\text{Na}$  can be measured by applying a Geiger-

Müller counter to the surface of the skin and thus detecting its penetrating gamma-rays, its distribution in the blood and extracellular tissue fluids can be followed. With this technique of measuring tissue vascularity it has been possible to assist in evaluating the blood supply prior to amputation. Similar investigations with the radioactive inert gases are reported by Tobias, Lawrence and Hamilton<sup>10</sup>.

The use of radiostrontium  $^{89}\text{Sr}$  for the therapy of bone malignancies has been suggested on several occasions because of the concentration of this element in bone analogously with calcium. Its use was first suggested by the late Dr. Charles Pecher<sup>108</sup>. A comprehensive report on this material is still to be published. Actually, however, it is unlikely that diffuse irradiation of bone and marrow for relatively localized malignant growths will prove of much value, particularly in view of the danger of marrow depression. Nevertheless beneficial results have been obtained in the treatment of metastatic prostate cancer in the way of slowing down of the malignant process and control of pain (Lawrence<sup>74</sup>).

A number of radioactive colloids have been used in preliminary therapeutic studies. These include, as already mentioned, anhydrous chromic phosphate, which localizes almost entirely in the liver and spleen<sup>67</sup>; colloidal  $\text{MnO}_2$  protected by gelatin<sup>48, 126</sup>; zinc suspended in a suitably prepared solution of



pectin<sup>102</sup>; colloids of several elements, radioisotopes of which occur as fission products ( $^{39}\text{Y}$ ,  $^{40}\text{Zr}$ , and  $^{41}\text{Nb}$ )<sup>22, 23, 68</sup>; and colloidal sols of gold<sup>40a, 125a</sup>. The fission colloids may, depending upon the method of preparation, concentrate almost exclusively in the liver and spleen or go in equal concentration into the bone marrow<sup>22, 68</sup>. Because of the relative abundance of  $^{39}\text{Y}$ ,  $^{40}\text{Zr}$ , and  $^{41}\text{Nb}$  in fission, there is a potentially rich source of their radioactive species for such investigations and for possible widespread

clinical application. Investigations with radiomanganese as labeled colloidal manganese dioxide in an aqueous medium with gelatin as a protective colloid have recently been reported by Hahn and Sheppard<sup>48, 126</sup>. These authors suggest the possibility that this material may be localized upon intravenous injection in the lymphoid reticuloendothelium. More recently Sheppard, Goodell, and Hahn<sup>125a</sup> have suggested the use of gold sols labeled with  $^{198}\text{Au}$  for this purpose.

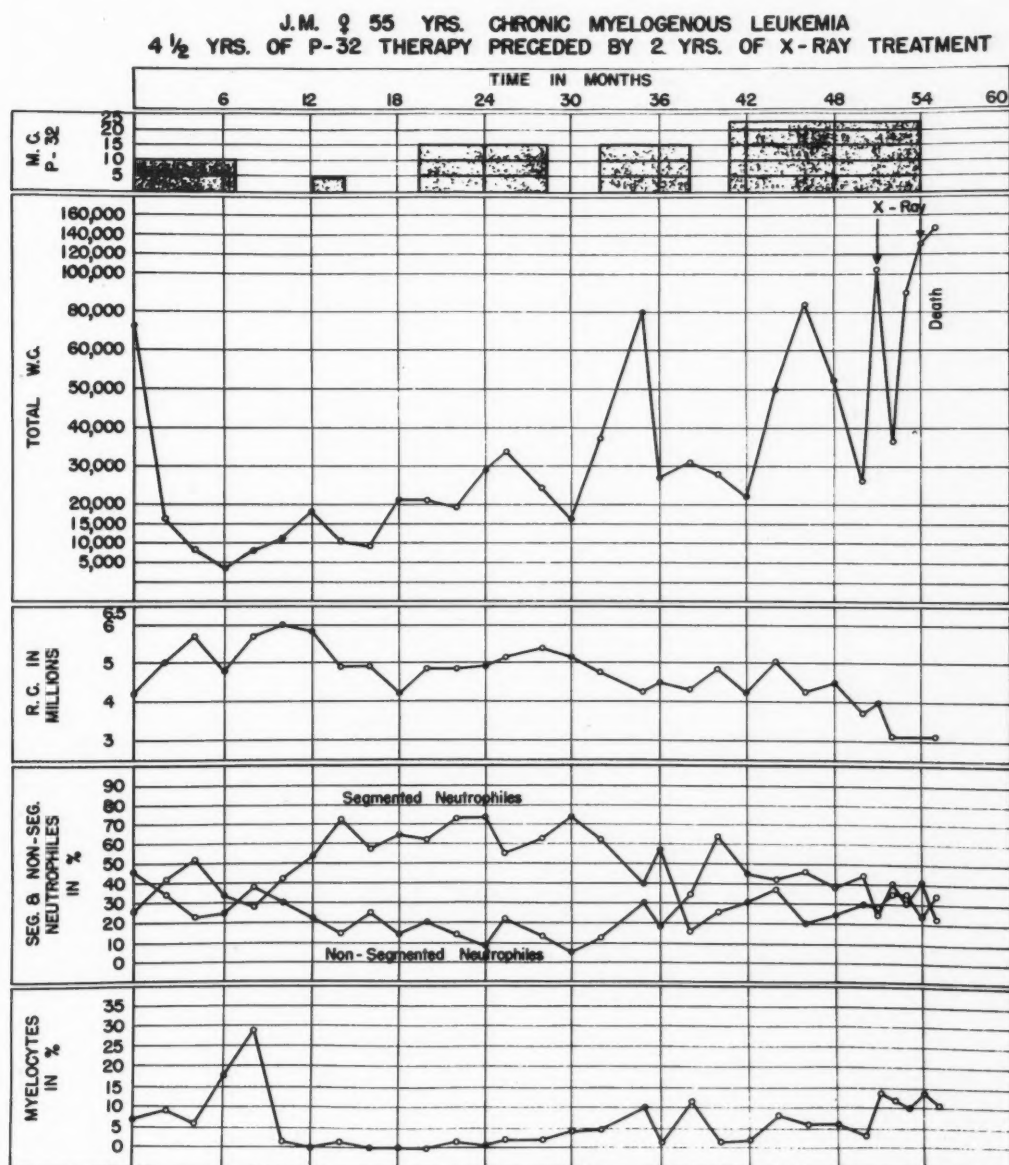


Figure 5.—Chronic myelogenous leukemia. Satisfactory response to therapy for four years, then failure to respond to further treatment.

## A.A. 33 YEARS. POLYCYTHEMIA VERA WITH MARKED LEUKEMOID REACTION.

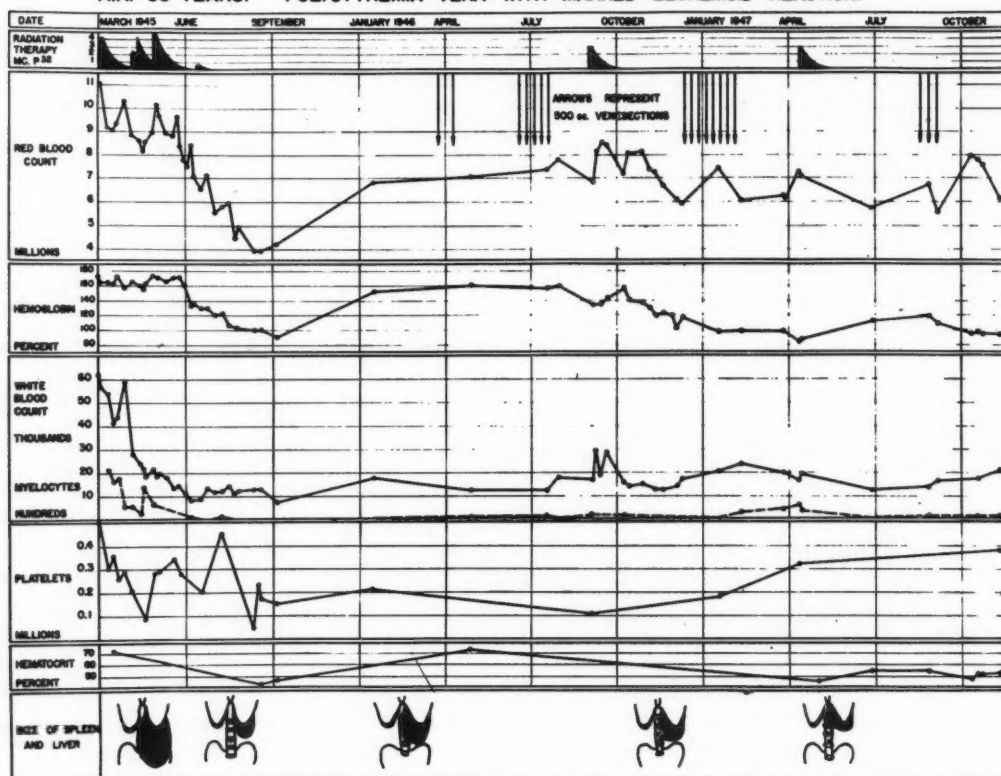


Figure 6.—Polycythemia vera with leukemic blood picture prior to treatment with  $P_{32}$ . The elevated red blood cell count has been controlled with some difficulty, but the leukemic blood picture has been suppressed up to the present time (June 1948). The patient has been relatively symptom-free during this three-year period.

In addition to the intravascular use of these colloids there are also, as mentioned, possible applications in interstitial infiltration of malignant growths, (Allen *et al.*<sup>2</sup>). Müller<sup>102</sup> has recently reported on the use of  $^{30}\text{Zn}$ , a short-lived isotope of 38.3 minutes half-life, in the interstitial injection of uterine carcinomata (2 cases) in a pectin-protected suspension of  $^{30}\text{Zn}$ ; he reports the strict localization of the isotope in the region of inoculation during the period of its effective activity and a tissue reaction similar to that following  $^{88}\text{Ra}$  therapy. Hahn *et al.*<sup>104</sup> have given encouraging accounts of the clinical applications of gold sols containing  $^{79}\text{Au}^{198}$  and given interstitially and intraperitoneally in the treatment of certain malignant growths. In general the use of labeled colloidal materials is promising and deserves thorough clinical trial. It is a step in the direction of selective irradiation therapy.

Although  $^{32}\text{P}$  and  $^{53}\text{I}$  radioisotopes are the only artificial species for which therapeutic applications have been proven, it seems quite likely that in a few years a number of different isotopes will have well accepted clinical uses. In addition to the elements already mentioned there are important possibilities in the labeling of organic compounds with long-

lived radiocarbon— $^{14}\text{C}$ —and radiohydrogen or tritium— $^3\text{H}$  or  $\text{T}$ . If radiation is ever to prove a vital tool for the palliation or cure of malignancy, the only possible way to accomplish this end would seem, from our present perspective, to be the discovery of organic substances which undergo highly selective localization in various types of cancer cells in contrast to those of normal tissue and which can be labeled with a suitable radioisotope.  $\text{T}$ , with the low penetrating power of beta-rays and its rapid turnover in the body, is particularly interesting in this regard. If it can be put in relatively stable positions in localizing compounds, it will expend most of its ionizing power within the concentrating cells. Potentially it is an ideal radiotherapeutic agent.

A discussion of radiotherapy with isotopes would not be complete without mention of fissionable isotopes—i.e., of uranium— $^{235}\text{U}$ —and plutonium— $^{239}\text{Pu}$ —and of other isotopes that release large amounts of ionizing radiation upon being bombarded with slow neutrons—i.e., of lithium— $^6\text{Li}$ —and boron— $^{10}\text{B}$ . If these materials can be localized in given tissues and organs and the region bombarded with slow neutrons, a significantly higher radiation can be conferred on the isotope-containing

tissue than on the normal or uninvolved tissue through which the neutrons also must pass. Kruger<sup>73</sup> has shown that pieces of transplantable mouse tumor soaked in boric acid solution and then irradiated *in vitro* with slow neutrons before inoculation into new hosts showed a significantly lower percentage of "takes" than control tumor pieces soaked in boric acid but not irradiated. Zahl, Cooper, and Dunning<sup>153</sup> have shown that, if  $^6\text{Li}$  or  $^{10}\text{B}$  salts are infiltrated into mouse tumors *in vivo* and the host animals bombarded with slow neutrons, there is a significant increase in tumor regression over that in bombarded, but uninjected controls. Recent work of Tobias, Weymouth, Wasserman, and Stapleton<sup>142</sup> on the effect of colloidal  $\text{UO}_2$  enriched with  $^{235}\text{U}$  concentrated in the liver and spleen of mice and there subjected to slow neutron bombardment also clearly shows the enhanced effect of radiations when nuclear disintegration processes of high energy are induced in tissues. It is interesting to note that these workers observed a greater biological effect per unit of tissue ionization with fission recoils than with beta particles. There seems little chance, however, that such studies will ever lead to therapeutic applications because of the short mean free path of thermal neutrons, the damaging effects of the infiltrating neutrons, and the toxic effects of fissionable materials.

Finally there should be mentioned the possible therapeutic use of charged nuclear particles—protons ( $p$ ), deuterons ( $d$ ), and alpha particles ( $\alpha$ )—of high energies from the cyclotron and other heavy particle accelerators. This would be an isotopic application of sorts inasmuch as the nuclei of single species of hydrogen ( $^1\text{H}$ ) and helium ( $^4\text{He}$ ) are being employed. None of these has been used clinically as yet. But recently Wilson<sup>150</sup> has suggested the possibility that very high energy protons—of 100 Mev or more—produced by the giant cyclotrons might find use in direct beam radiotherapy. The 100 Mev proton would produce its maximum ionization some centimeters beneath the skin and thus might be used to radiate deep-lying lesions, especially where the skin tolerance is a limiting factor. A comparable, although non-isotopic, application of accelerated particles might be the use of high energy electrons from the betatron as suggested by Kerst<sup>71</sup> and Quastler<sup>110</sup>. Also deuterons may be used to produce fast neutrons from beryllium ( $^9\text{Be}$ ); these and other neutrons have been used in a number of studies on the biological effects of irradiation (Aebersold and Lawrence<sup>1</sup>; Stone and Larkin<sup>152</sup>).

In summary it may be observed that the role in therapy of radioactive isotopes and of those stable species that can also be adapted to the production of ionization in tissues is still in a primitive stage of development. Unquestionably, the future will see great expansion in our knowledge of their usefulness and practical application. The use of the new types of radioactivity must, however, be approached with caution. It has long been known that ionizing radiation in addition to its acute effects may have such chronic manifestation as the induction of malignant change in tissue. Radium-induced bone sarcoma

have been observed for many years. Recently Lisco, Finkel, and Brues<sup>86</sup> have shown that both radiostrontium— $^{90}\text{Sr}$ —and plutonium— $^{239}\text{Pu}$ —can produce bone tumors in mice, particularly the former. This has particular significance for the possible use in man of long-lived isotopes of elements that concentrate in bone—as for example, many of the fission product elements.

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## California Cancer Commission Studies\*

### Chapters XIX and XX

# Carcinoma of the Stomach

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THE yearly deaths from carcinoma of the stomach number approximately 45,000. It is estimated that 10,000 of the patients who die might be saved if they were operated upon early. Treatment by x-ray and radium is of no value. *Cancer of the stomach cannot be cured except by removal of the growth.*

Cures of cancer of the stomach will increase only with its earlier recognition. Its onset is insidious, usually with few symptoms, and there is no single group of symptoms which is absolutely characteristic. Certainly any person 35 years of age or over who has indigestion of more than one week's duration should be suspected of having carcinoma of the stomach. A short history of indigestion in an older man is an alarming symptom, even without a palpable mass. Symptoms of obstruction may indicate a tumor occurring at the outlet of the stomach. Chronic indigestion, loss of weight or strength or both, or vomiting of blood or any material that looks like blood, indicate the need for careful investigation. Do not wait for the appearance of these symptoms before investigation, because some of them may indicate already advanced disease.

When carcinoma of the stomach is suspected, it is up to the doctor, with the cooperation of the patient, to do everything possible to prove or disprove this diagnosis. A careful physical examination must always be done. This should include a rectal examination, since one of the first findings in carcinomas of some types is a so-called rectal shelf—which, however, indicates incurable disease.

A careful x-ray examination, particularly fluoroscopic examination, should be done by a qualified radiologist to determine the possibility of a filling defect, or an irregularity or rigidity of a portion of the stomach. It should be stressed that *if the roentgen examination is negative, a patient with continued symptoms referable to his stomach should have a repeat examination after a period of two weeks, regardless of whether or not he is on any sort of special diet.*

A routine blood count is important. Many patients with indigestion have a moderate to severe secondary anemia. Too many are treated for an indefinite period for an unexplained secondary anemia. *Any unexplained secondary anemia means either carcinoma of the stomach or carcinoma of the right colon until this is absolutely disproved.* A gastric analysis is in-

formative, as an achlorhydria would point toward, but not necessarily clinch, the presence of cancer of the stomach. Achlorhydria is found in 60 per cent of patients with carcinoma of the stomach.

Every patient with pernicious anemia should have a fluoroscopic examination of the stomach yearly, since approximately 8 per cent of these patients develop cancer.

Gastroscopy, *in competent hands*, may be of value in differential diagnosis.

Too often doctors tell their patients that nothing can be done for cancer of the stomach. This pessimistic attitude is all wrong. Necropsy data show that over 20 per cent of persons dying of cancer of the stomach have a lesion which is still confined to the stomach. *An exploratory operation should be done in every case of cancer of the stomach unless distant metastases are unequivocally demonstrated.* A resectable lesion is frequently found at operation, even though preoperative examination reveals a large, bulky tumor palpable in the upper abdomen, a large filling defect shown by x-ray, achlorhydria and secondary anemia. Some of these patients live well beyond the five-year survival period. *The surgeon must always be prepared to do an extensive and drastic procedure.* (Plate I.) What is inoperable in the hands of an inexperienced surgeon may be resectable in other hands. In some cases even when there is metastasis, a palliative operation may afford the patient relief for a considerable time. The operative technique and preoperative and postoperative care of these patients have been developed to a very high degree. Subtotal or total resection of the stomach for carcinoma should be carried out with a mortality rate of 10 to 15 per cent, or less in special clinics.

It is known, of course, that the five-year survival rate in all cases of cancer of the stomach is very low (10 to 15 per cent). A tumor occurring at the outlet of the stomach may cause symptoms of obstruction leading to an early diagnosis, and for this group the five-year survival rate is higher (18 per cent). Doctors in general should keep in mind that the only way to increase the survival rate for carcinoma of the stomach is to make the diagnosis *early* while the lesion is still localized in the stomach. Livingston and Pack as well as Walters, Gray and Priestley have shown that if gastric resection can be done when the carcinoma of the stomach is entirely confined to that organ the five-year survival rate reaches 55 per cent.

\*Organized by the Editorial Committee of the California Cancer Commission.





Figure 1.—Roentgenogram of 56-year-old man with history of ulcer for two years. Films were read as showing a prepyloric ulcer. Medical treatment prescribed. 1941.



Figure 3.—Same patient as Figure 1 and 2, 1946. Radiologist, patient, and patient's physician all agreed that he now had cancer of the stomach. How much better if surgery had been done in 1941 or 1943, instead of 1946!



Figure 2.—Same patient as in Figure 1, 1943. Medical treatment continued.

The relationship of ulcers of the stomach to carcinoma is a question that frequently arises. Any gastric ulcer is liable to suspicion until proved benign. We know that some carcinomatous ulcers of the stomach will show evidence of healing on a medical regimen (See Figures 1, 2, 3). Any gastric ulcer that does not improve markedly and practically disappear in two weeks under medical treatment should be operated upon and a subtotal gastric resection done with removal of one-half to three-fourths of the stomach, giving the ulcer a very wide margin. About 18 to 20 per cent of gastric ulcers which are thought to be "benign" are found, on microscopic examination, to be carcinoma. The five-year survival rate in these cases is 40 to 60 per cent.

Other gastric tumors that might be considered are lymphosarcoma, leiomyoma, and polyps. Polyps in the stomach are definitely precancerous lesions; therefore, they should be removed either by local excision or by subtotal gastric resection. The leiomyomas are not usually malignant, but may undergo malignant changes; while they are not usually diagnosed preoperatively, any tumor in the stomach should be removed surgically if possible. Lymphosarcoma of the stomach, if localized, should be removed surgically. Again the tumor is not usually diagnosed specifically before operation. Lymphosarcoma does respond, at least for a period of time, to x-ray therapy; so if there is an extensive involvement

of the stomach with regional spread, a biopsy should be taken to prove the diagnosis but no further surgery should be done. The patient should then be sent to a competent radiologist for radiation therapy.

#### SUMMARY

Cancer of the stomach is a frequent malignant lesion. Any persistent indigestion in an individual over 35 years of age—particularly a male, as cancer is more frequent in males than in females—indicates

the need for a physical examination and x-ray and laboratory studies either to demonstrate or rule out a carcinoma of the stomach. The only treatment for carcinoma of the stomach is complete excision of the tumor with a wide margin of normal tissue. *The only hope for increasing the number of cures of carcinoma of the stomach is the earlier recognition and earlier surgical treatment of this disease.* The pessimism of so many doctors is wrong. It causes delay and destroys the only chance of a cure by early operation.

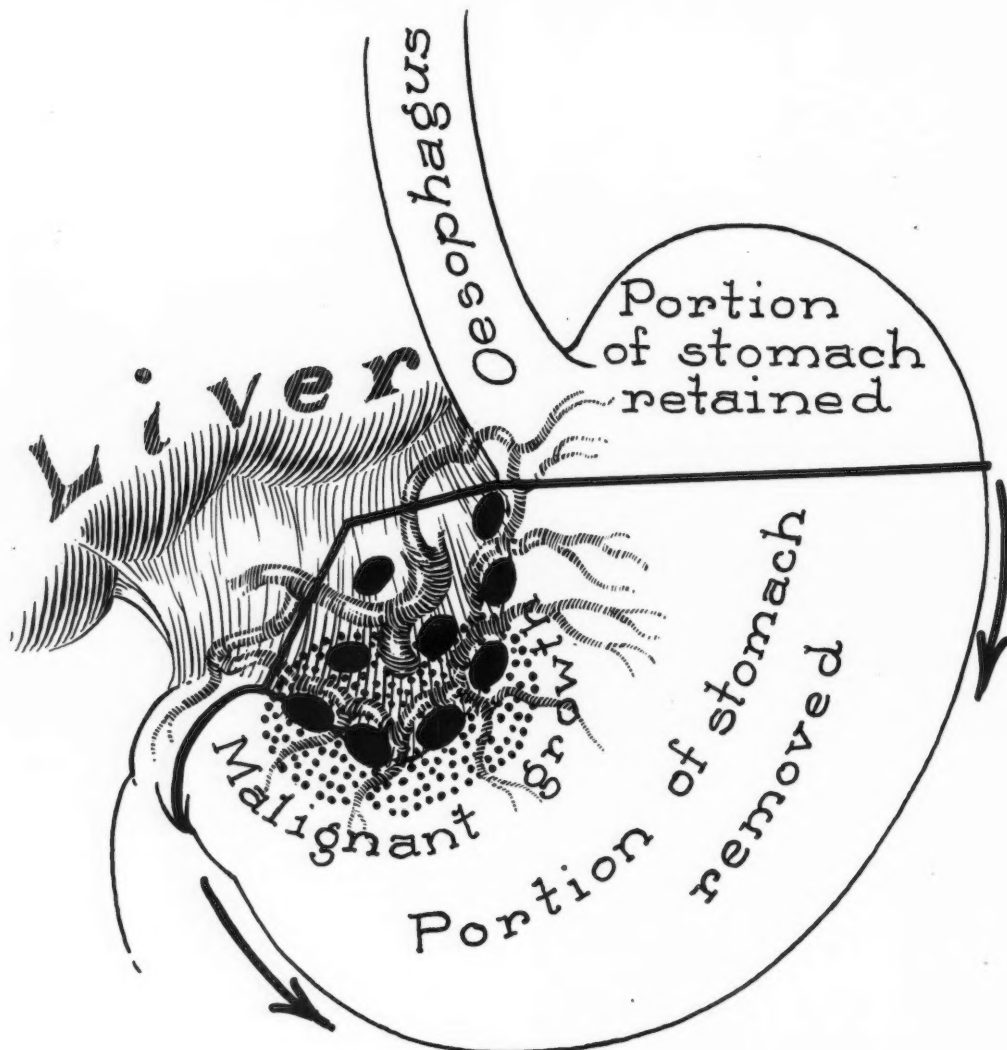


Plate I.—Showing the amount of stomach which should be removed for the ordinary carcinoma of the stomach. In carcinoma higher up, a total resection should be done. The entire lesser curvature and lesser omentum, as well as the greater omentum, should be removed.

## Carcinoma of the Colon

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THERE are approximately 30,000 deaths in the United States each year from carcinoma of the colon and rectum. These comprise 17 per cent of all deaths due to cancer. Nevertheless, the possibility of permanent cure is greater for cancer of the large bowel than for cancer anywhere else within the body. In many of the larger clinics the resectability rate is now between 80 and 90 per cent, the operative mortality is well below 10 per cent, and the five-year non-recurrence rate is better than 50 per cent. This represents five-year "cure" in about one out of every three patients. During the past 15 years considerable progress has been made in surgical technique, in anesthesia, and in preoperative and postoperative care. Yet during the same period of time there has been no appreciable lessening of the time interval between the onset of symptoms and the establishment of diagnosis. This interval continues to average between eight and nine months. *Curability is directly related to early diagnosis. The opportunity for early diagnosis belongs largely to the general practitioner who is first consulted for symptoms which are seldom pathognomonic of large bowel neoplasm, but which should always create suspicion of such disease.*

### SYMPTOMATOLOGY

There are no pathognomonic symptoms upon which to base an early diagnosis of carcinoma of the colon. However, there are usually symptoms which direct attention to the bowel and demand careful investigation.

**Right Colon:** Primary function of this portion of the colon is absorptive. The lumen of the bowel there has its greatest diameter and the contents of it are liquid. Symptoms, therefore, are primarily the result of physiologic disturbance, and obstructive symptoms are uncommon. Tumors in this area are usually large, cellular, and ulcerated. Toxic products are readily absorbed, producing constitutional symptoms of anemia, weight loss, and fatigue. Abdominal distress of some kind is usually present. There may be a sensation of fullness, of weight, or of tightness in the right side of the abdomen. Cramps or indefinitely localized pain may occur. Not infrequently the patient himself has discovered a palpable mass. Fewer than half of the patients will have had any noticeable change in bowel habits. Mild diarrhea is twice as common as increasing constipation. Only 10 to 20 per cent have gross blood in the stools.

**Left Colon:** Primary function here is storage. Constitutional symptoms are conspicuously lacking. Any marked anemia or weight loss is suggestive of metastases. The patients frequently exhibit an appearance of vitality and well-being which belies the serious nature of the disease responsible for the apparently minor symptoms for which the doctor is often apologetically consulted. The dominant symptoms are change in bowel habits and bleeding. Most frequently there is increasing constipation, with minor ab-

dominal cramps and variable distention. About one-third of the patients describe an increased frequency of stools. Less commonly there is a true diarrhea, with numerous watery stools daily. Alternating constipation and diarrhea does occur, but in only a small percentage of patients. Occasionally there is a sudden initial onset of complete obstruction with no prodromal symptoms. Blood in the stools is noted by about 50 per cent of patients. This may consist of only occasional streaks of bright red blood, or there may be larger amounts of bright or dark red blood sometimes with the passage of clots. Episodes of severe gross hemorrhage may occur.

### DIAGNOSIS

Evidence of weight loss and anemia may be observed in patients with carcinoma of the proximal colon. A palpable tumor may be present. These signs are rarely evident in lesions of the distal colon until a late stage in the disease. Abdominal distention may be present in lesions of the descending colon and sigmoid, but seldom is this evident in the early stages. The liver edge should always be palpated carefully for evidence of metastases. Localized signs of peritoneal irritation, simulating appendicitis or diverticulitis, may be present when the lesion is complicated by penetrating infection. Secondary abscess formation may occur, with classical symptoms and signs which entirely overshadow the underlying neoplasm.

*Digital examination of the rectum is of greatest importance in diagnosis of carcinoma of the rectum.* Furthermore, some tumors of the sigmoid, too high up to be directly palpated through the lumen of the bowel, may be felt through the rectal wall in the cul-de-sac, into which the tumor may have gravitated by its own weight. Occasionally such a lesion, still resectable, is thought to be due to peritoneal implants in the cul-de-sac and considered inoperable.

Sigmoidoscopic examination is of great value, not only for direct visualization of tumors of the rectum and lower sigmoid, but to rule out non-malignant ulcerative disease, and at times to verify the fact that blood is actually coming from higher up in the colon.

The actual diagnosis of lesions beyond reach of the sigmoidoscope depends largely upon x-ray examination by barium enema. It should be emphasized that such examination, even with the best technique, has a diagnostic accuracy of only about 90 per cent. Even large carcinomas are not always demonstrated, especially in the region of the colon flexures, or where redundant loops of sigmoid mask the critical area. *A second and even third examination is indicated when the clinical evidence points toward a diagnosis of carcinoma.* Instances do occur in which the diagnosis is made only by exploratory laparotomy after repeated negative x-ray findings. The criteria for x-ray diagnosis include persistent obstruction to the flow of barium in spite of manipulation and change of position of the patient, or a persistent filling defect

which may be annular or polypoid. The introduction of air or oxygen into the colon after evacuation of the barium enema is of particular value in the demonstration of polypoid lesions.

A "gastro-intestinal series," in the meaning of the term as it is commonly used, actually is only diagnostic of lesions in the stomach and duodenum. The colon is not visualized in sufficient detail to permit the diagnosis of intrinsic lesions. Satisfactory examination of the colon demands barium enema examination.

Stool examinations are useful to rule out parasitic disease. The presence of parasites, however, does not necessarily rule out malignancy. The presence of occult blood in the stool deserves every consideration as a sign of suspicion, but is not necessarily pathognomonic of neoplasm. The presence of gross or occult blood in the stool does make it mandatory that cancer be thoroughly searched for.

#### DIFFERENTIAL DIAGNOSIS

*Right Colon:* Symptoms may simulate those of peptic ulcer, carcinoma of the stomach, cholecystitis, and tumors or inflammatory lesions of the kidney. Tuberculosis and regional colitis may produce symptoms and roentgenologic signs similar to those of carcinoma. In the case of carcinoma, barium enema examination usually shows a relatively shorter segment of bowel involvement, with a more sharply delineated filling defect. In tuberculosis there is usually an active pulmonary lesion. Amebic granuloma, though rare, may closely simulate carcinoma. Appendicitis, and particularly appendiceal abscess, may be easily confused with carcinoma of the cecum. Differentiation by x-ray examination is usually but not always possible.

Carcinoma of the proximal colon ranks in importance with carcinoma of the stomach as a cause of secondary anemia. A diagnosis of unexplained secondary anemia without x-ray examination of the stomach and colon is fraught with tragedy.

*Left Colon:* Differentiation of diverticulitis and carcinoma is a recurring and oftentimes difficult problem. Carcinoma complicated by inflammation or abscess formation may produce the classical symptoms and signs of diverticulitis with pain, fever, leukocytosis, and localized signs of peritoneal irritation. Diverticulitis may produce obstructive symptoms and in some instances bleeding, with none of the signs or symptoms of inflammatory disease. Differentiation by barium enema examination is often difficult, sometimes impossible. Comparative studies of numerous films are of the greatest value. The filling defect of a carcinoma tends to remain constant, while the narrowing and irregularity due to diverticulitis are less constant, with some variability in the diameter of the lumen and the contour of the defect. Diverticulitis may produce an inflammatory tumor which is not only indistinguishable from carcinoma by x-ray examination but may be so even on surgical exploration. A carcinoma may at times be entirely overshadowed by deformities due to diverticulosis and diverticulitis. Although bleeding does occur at times in diverticular disease, this symptom should

always suggest the possibility of coexisting carcinoma.

A diagnosis of chronic ulcerative colitis as the explanation of symptoms of diarrhea and bleeding is never justified without confirmation of the actual existence of the disease by proctoscopic examination.

Irritable colon, with symptoms of bowel irregularity, requires differentiation by x-ray examination. Segmental spasm may simulate the filling defect of carcinoma, but the defect tends to be inconstant in repeated films.

Fecal impactions may produce obstructive symptoms or extreme diarrhea. Their presence may result in apparent filling defects on x-ray examination. Digital examination of the rectum will immediately determine the presence of rectal impaction. After the elimination of all impacted stool there may be spectacular cessation of symptoms, and apparent filling defects may entirely disappear on repeat x-ray examination.

Pelvic tumors of inflammatory or neoplastic origin may compress the sigmoid, producing symptoms referable to the bowel. Endometrioma may involve the wall of the bowel and may cause rectal bleeding. The majority of such lesions occur at a level which can be reached with a sigmoidoscope. Visualization of an intact mucosa at the site of such a tumor should prevent a mistaken diagnosis of carcinoma of the bowel.

*One should not be misled by the presence of hemorrhoids. When there is bright red blood in the stool one must always rule out cancer of the colon first.*

#### TREATMENT

There is but one curative treatment for carcinoma of the colon, and that is radical surgical excision of the involved segment of bowel together with wide removal of the corresponding area of lymphatic drainage and regional lymph nodes. Successful operation depends largely upon the technical skill of the surgeon. A thorough understanding of the problems of blood supply to the colon is imperative. Much depends upon the judgment of the surgeon in the proper choice of the best method of surgical treatment to be used in each individual case. There are proper places for single stage and multiple stage operations, for primary anastomosis by an open or closed method, for end-to-end or side-to-side or end-to-side anastomosis and for obstructive resection based upon the Mikulicz procedure.

Adequate preoperative preparation is of the greatest importance, including measures for mechanical decompression of the colon, correction of vitamin and protein deficiencies, transfusion, and attention to control of any coexisting disease. The use of sulfasuxidine and sulfathalidine is a valuable adjunct to preoperative preparation. It should be recognized, however, that these drugs by no means eliminate any of the possible complications of surgical operation, and that their use permits no relaxation of the principles or precautions necessary for success.

Postoperative care is directed toward the avoidance and control of potential complications and toward early restoration of adequate nutrition.



Due consideration should be given to the psychological problems which are incurred by the patient with cancer. Optimism and assurance are justifiable on the basis of the relatively high possibilities of cure. Following recovery from successful surgical extirpation, repeated reassurance is frequently necessary for the peace of mind and physical welfare of the patient. Minor subjective complaints, or the development of symptoms of entirely unrelated illness may convince the patient that he is hopelessly riddled with cancer. This incorrect assumption is occasionally made by the doctor. While such a possibility must necessarily be kept in mind by the physician, acceptance of the fact should never precede the establishment of definite evidence that metastases are present.

The recurrence of symptoms of bowel irregularity or of bleeding are not presumptive evidence of recurrence of cancer. The incidence of development of new primary lesions is sufficiently high to suggest this possibility. In such an event, the prognosis for cure by surgical excision of the new lesion is equally as favorable as it was for the first lesion.

#### SUMMARY

1. Carcinoma of the colon and rectum is responsible for 17 per cent of all deaths due to cancer.
2. The possibility of cure is greater for cancer of the large bowel than for cancer anywhere else within the body.
3. Curability is directly related to early diagnosis.
4. There are no pathognomonic symptoms upon which to base an early diagnosis. However, unexplained secondary anemia, change in bowel habits, or blood in stools demands careful investigation of the large bowel.
5. A complete physical examination should be done. In addition a digital palpation of the rectum, sigmoidoscopic inspection and x-ray examinations with barium enema are necessary.
6. The one curative treatment is radical surgical excision.

#### POLYPS OF THE COLON

The colon and rectum are a frequent site for the development of polyps. There is abundant evidence that the vast majority of these tumors are precancerous lesions. Their discovery and destruction will prevent carcinoma in many instances. Polyps may develop at any age. They are the commonest cause of intestinal bleeding in children. Probably 4 per cent of adults harbor one polyp or more in the large bowel. They may occur singly, or there may be a few or great numbers. Multiple polyposis is frequently but not always a familial disease. About 10 per cent of patients with chronic ulcerative colitis develop multiple polyps, a condition which has been called pseudopolyposis because of the inflammatory origin of the lesions. These, too, are precancerous lesions.

Polyps produce no symptoms until surface ulceration results in bleeding or until there is mechanical interference with bowel motility. By far the commonest symptom is bleeding. There may be gross hemorrhage, but in the vast majority of cases the only symptom is streaking of blood on the stool.

Diagnosis is achieved by sigmoidoscopic examination of the lesions within reach with this instrument. Higher lesions must be identified by x-ray examination. Routine opaque enema examination is inadequate in the majority of cases. Air contrast examination, by inflation of the colon with air or oxygen after partial evacuation of the barium mixture, is the only satisfactory diagnostic procedure. Even with the most skillful technique of examination these tumors are often difficult to visualize. A second and a third examination may be necessary. Occasionally diagnosis can be established only by exploratory laparotomy and careful palpation of the colon. This becomes a justifiable procedure when repeated examination fails to demonstrate the origin of obvious continued bleeding from the colon.

The treatment of polyps of the colon is surgical removal. Lesions within reach through a sigmoidoscope may be removed through this instrument by diathermy snare if they are pedunculated, or by electrofulguration when sessile in character. The danger of perforation of the bowel wall must be recognized and avoided. All single polyps higher in the colon should be removed by laparotomy and colectomy. Treatment of multiple polyposis of the colon should consist of preliminary eradication of all polyps of the rectum, followed by ileoproctostomy and colectomy. When malignant degeneration has already occurred in the rectum, complete colectomy with permanent ileostomy is the recommended procedure. This is also the proper treatment for polyposis secondary to chronic ulcerative colitis.

When a polyp of the colon is removed by colectomy, immediate frozen-section microscopic examination is advisable, since polyps whose gross characteristics are those of a benign lesion may prove to be malignant, at times with regional glandular metastasis already present. When definite malignant degeneration has already occurred, radical resection comparable to that which would be done for more advanced carcinoma should be performed. The absence of evidence of carcinoma in the pedicle of a malignant polyp does not preclude the existence of regional glandular metastasis.

#### SUMMARY

1. Many if not all carcinomas of the colon and rectum originate in benign adenomatous polyps.
2. Discovery and removal of benign polyps will prevent the development of carcinoma in many instances.
3. The cause of rectal bleeding should never be assumed to be hemorrhoids. Proper examination to determine the source of bleeding includes anoscopic, sigmoidoscopic and barium enema examination, with air contrast study in all cases in which the cause of bleeding has not been otherwise established.

"Cancer of the Rectum," by W. H. Daniels, M.D., Chapter XXI of the California Cancer Commission Studies, will appear in this section of the August issue of CALIFORNIA MEDICINE.

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## EDITORIALS

### The C.M.A. Expands

Announcement by the Council of the California Medical Association at the 1948 Annual Session that the opening of a Southern California office had been approved was cause for satisfaction to many Association members in the southern counties. Quite naturally, some of them had previously felt that the San Francisco headquarters were a long way off, in miles if not in spirit.

It is now possible to announce the opening of a Southern California office in the Subway Terminal Building, Los Angeles. Interestingly enough, the room number is 606. This office serves not only as a Southern California headquarters but is available for the use of Association employees and officers, as well as the Cancer Commission and other committees of the Association.

Coincident with the Council's decision to open this office comes the announcement that Mr. Ed Clancy has been employed as Field Secretary. Mr. Clancy is a former newspaper publisher in Ventura County and is well versed and experienced in the fields of public relations and legislation. For the past three years he has served the Association through employment by public relations counsel and has proved his value to the Association in numerous counties where

he managed the "Voluntary Health Insurance Weeks" which were a major part of the overall public relations program. More recently he has gone into several counties, on request, to aid in establishing proper public relations for county societies which were faced with unusual problems.

The opening of a Southern California office and the employment of a field secretary are indicative of the expanding activities of the Association. The permanent headquarters staff now numbers nine, with a part-time director of postgraduate activities and a medical director of the Cancer Commission in addition. The addition of a field secretary brings the Association's total staff to twelve members and places the organization in a better position to serve its component county societies and their members. The growing problems of organized medicine, particularly in fields apart from scientific medicine, demand that an adequate staff organization be maintained, and it is obvious that the present personnel, both in numbers and in varieties of skills, is in a better position to do the job that needs doing.

The county societies and their members are cordially invited to avail themselves of the Association's services.

# CALIFORNIA MEDICAL ASSOCIATION

E. VINCENT ASKEY, M.D.	President	EDWIN L. BRUCK, M.D.	Council Chairman
R. STANLEY KNEESHAW	President-Elect	L. HENRY GARLAND, M.D.	Secretary-Treasurer
LEWIS A. ALESEN, M.D.	Speaker	SIDNEY J. SHIPMAN, M.D.	Chairman, Executive Committee
DONALD A. CHARNOCK, M.D.	Vice-Speaker	DWIGHT L. WILBUR, M.D.	Editor
JOHN HUNTON	Executive Secretary		

## NOTICES AND REPORTS

### Imperial County Postgraduate Seminar

The C.M.A. Postgraduate Committee reports on the Imperial County Seminar held at El Centro, May 20 and 21:

#### MAY 20

8:00 p.m.—Cancer of the Cervix and the Fundus Uteri—William E. Costolow, M.D., Los Angeles.  
General Aspects of Cancer—Lyell C. Kinney, M.D., Chairman, C.M.A., Cancer Commission.

#### MAY 21

10:00 a.m.—Clinical Conference: (1) Rheumatic Fever; (2) Toxemia of Pregnancy.

#### AFTERNOON PROGRAM

Common Pediatric Problems Encountered in General Practice—Sam J. McClendon, M.D., San Diego.  
Modern Management of Common Obstetrical Problems—Ralph Hoffman, M.D., San Diego.  
Pitfalls in Gynecological Surgery—Charles Isham, M.D., San Diego.  
Panel Presentation—Office Gynecology, Pediatrics and Obstetrics.  
Discussion Period.  
Motion Picture: Normal Breech Delivery.

Sixteen members of the Imperial Medical Association attended the seminars. This is approximately 60 per cent of the membership.

The program provided an excellent summary of the recognized and accepted advances in the presented subjects and it was agreed that the committee and the physicians attending the seminars were particularly fortunate in obtaining a fine faculty. Dr. Costolow emphasized the importance of early diagnosis of cancer of the cervix and endometrium. The responsibility for this, he said, rests not only with the patient but also with the family physician whose attention to unusual symptoms, with immediate and definite diagnosis by proper physical examination and biopsy, will result in treatment of a larger percentage of cases in early stages where an 85 per cent cure rate can be expected. Dr. Kinney's discussion dealt with the increasing incidence of cancer coincidental with the extension of the life span of larger proportions of the population into the years of higher incidence of cancer. Fifty per cent of all cancer may be diagnosed by the family physician, Dr. Kinney said, and the other 50 per cent must be

promptly diagnosed with the help of consultation and special examinations.

Dr. McClendon pointed out that in California there are only 335 pediatricians to serve an expanding population of approximately 10,000,000 people. The majority of pediatric care, about 75 per cent, particularly in non-metropolitan areas must therefore be supplied by physicians in general practice, he said. He discussed pediatric problems most likely to confront general practitioners. Dr. Hoffman's paper on obstetrics presented many very vital advances in this field particularly in prenatal care, in anesthesia, and in solution of operative problems. Dr. Isham outlined the most important and frequently occurring gynecological diseases and discussed the present treatment of them through uses of chemotherapy, antibiotics and surgery.

Physicians who attended the seminars requested that others be offered in the area in the fall months.

### Executive Committee Minutes

*Tentative Drafts: Minutes of the 208th and 209th Meeting of the California Medical Association Executive Committee.*

The 208th meeting was called to order by Dr. Sidney J. Shipman, acting chairman, at 10 a.m., in Room 220, St. Francis Hotel, San Francisco, Wednesday, April 14, 1948.

#### 1. Roll Call:

Present were Doctors E. V. Askey, R. Stanley Kneeshaw, Lewis A. Alesen, Sidney J. Shipman, L. Henry Garland (ex officio), members of the Executive Committee, Dr. Dwight H. Murray, chairman of the Committee on Public Policy and Legislation, Mr. Ben H. Read, executive secretary of the Public Health League of California, Mr. Howard Hassard, legal counsel, Mr. John Hunton, executive secretary, and Mr. Ed Clancy of public relations counsel.

#### 2. Hospital District in Porterville:

Mr. Read discussed the situation in Porterville, where a hospital district is in process of formation and pressure is being put upon local officials to open

up the staff of the proposed hospital to various substandard practitioners. The local physicians have asked for assistance from the Association in public relations matters and on motion regularly made and seconded, it was voted to send Mr. Clancy to Porterville to survey the situation and report back to the Council with suggestions for assistance to the local members.

After further discussion of the potential dangers to high professional standards through formation of hospital districts and the use of federal or state funds as aids in hospital construction, the following resolution was made, seconded and unanimously adopted:

WHEREAS, Many California communities are in need of additional hospital facilities; and

WHEREAS, Federal and state funds are available in some cases to aid in the construction of such facilities; and

WHEREAS, Funds may also be obtained by private subscription, as has been done in many communities under properly organized campaigns; and

WHEREAS, Federal or state funds may be obtained only by following a prescribed procedure which may entail considerable delay and may place upon the hospital directorate many burdens of construction details, possibly including costly fixtures not considered essential by those who will use, own and operate the hospital; and

WHEREAS, The provision of state funds will place the receiving hospital in a position where demands may be made upon the hospital management to admit substandard practitioners to the hospital professional staff because public money has been used in aid of construction and any practitioner may claim with some cause that his patients are a part of the public; now, therefore, be it

*Resolved*, That the Executive Committee of the California Medical Association, the Council concurring, places itself on record as urging that funds for hospital construction be raised by private subscription and cautioning all physicians and communities to investigate carefully the disadvantages attached to the use of public funds for hospital construction, it being understood that in some instances the use of public funds may represent a necessity which permits no alternative; and be it further

*Resolved*, That copies of this resolution be forwarded to all component county medical societies so that these societies and their members may look into the possible disadvantages of using public funds for hospital construction and not be misled by the theory of "something for nothing."

Adjournment.

SIDNEY J. SHIPMAN, M.D., *Chairman*

L. HENRY GARLAND, M.D., *Secretary*

## 209th Meeting

The 209th meeting was called to order by acting Chairman Sidney J. Shipman in the Association's office at 11 a.m., Sunday, May 9, 1948.

### 1. Roll Call:

Present were Doctors Shipman, Askey, Bruck and Kneeshaw, members of the Executive Committee, Secretary Garland and Editor Wilbur, ex officio members, and Messrs. Hunton (executive secretary), Hassard (legal counsel), and Clem Whitaker, public relations counsel. Absent: Dr. L. A. Alesen (illness).

### 2. Organization of Committee:

Attention was called to the fact that the Executive Committee had not yet organized. Upon nomination duly made and seconded, Dr. Sidney J. Shipman was unanimously elected Chairman.

### 3. Hospital Construction:

Considerable discussion was held concerning the construction of hospitals with private, state and federal funds or available combinations of such funds. It was pointed out that the receipt of federal funds is through the State Department of Public Health, which designates a priority list for hospitals to receive the limited (about \$1,900,000 annually) federal hospital money available to the State of California. It was also pointed out that various construction specifications are imposed before federal funds may be received and that such specifications may result in an increased construction cost. Attention was also paid to the present lack of state laws which require the maintenance of professional standards in hospitals constructed under the Hospital District Law, this lack leaving such hospitals at the discretion of the local administrative board insofar as professional staff and operating standards are concerned.

It was regularly moved, seconded and unanimously voted that the Association adopt a program to (1) amend present state laws in order to insure high professional standards in hospitals constructed under the Hospital District Law, (2) carry on an educational program with county medical societies and their members relative to the advisability of raising hospital funds by private subscription and the possibilities of impaired professional standards where public moneys are obtained for hospital construction, and (3) work toward the elimination of substandard health insurance policies now reported being sold in quantity in California.

### 4. Osteopathy:

It was reported to the committee that the California Osteopathic Association has an active committee engaged in studying the possibility of a merger of medicine and osteopathy in California, that a new osteopathic school has sprung up in the state and is issuing M.D. degrees and that at least some of the osteopathic leaders in California are interested in a possible professional merger. On motion duly made and seconded, it was voted that Doctors Askey and L. A. Alesen be authorized to meet with members of the committee of the California Osteopathic Association for informal discussions of this matter.

### 5. Los Angeles Office for C.M.A.:

Mr. Hunton reported on his investigations into available office space in Los Angeles and stated that



the major medical buildings there were not able to offer suitable space at this time. He also reported that Mr. Ed Clancy of Mr. Whitaker's office now has an office in Room 606 of the Subway Terminal Building in downtown Los Angeles, with telephone answering and stenographic service available through a public stenographer from whom the office space is rented. Mr. Clancy's services have recently been in demand for legislative purposes for the Association and the Committee on Public Policy and Legislation has outlined additional work for him that will extend for a year or more. Mr. Hunton suggested, and Mr. Whitaker agreed, that under the circumstances it would be advisable for the Association to place Mr. Clancy directly on its payroll and divide his duties between legislative work and field secretarial work out of the Los Angeles office.

On motion duly made and seconded, it was unanimously voted that Mr. Clancy be employed by the Association, with headquarters in Los Angeles, and that the office he now occupies be assumed by the Association as its Los Angeles office for the use of Association employees, including the Cancer Commission.

#### 6. Definition of Public Health:

The Chairman and members of the committee discussed the proposal that a definition of the scope of

recognized public health activities and a delineation between public health and the private practice of medicine be arrived at. After discussion it was regularly moved, seconded and voted unanimously that such a definition be undertaken in cooperation with Dr. Wilton L. Halverson, State Director of Public Health.

#### 7. Proposed A.M.A. Resolution Re Rebates:

A letter was read from Dr. Wilbur Bailey, in which he proposed that a resolution be introduced into the A.M.A. House of Delegates by the delegates from California in an attempt to clarify possible misunderstandings regarding rebating practices. It was brought out that the A.M.A. now has a committee studying rebating questions and that Dr. E. Vincent Askey is a member of that committee. It was regularly moved, seconded and voted that legal counsel prepare a letter to this committee, requesting that the committee introduce a resolution into the A.M.A. House of Delegates to establish as a part of the Principles of Medical Ethics a definition of rebating which could be applied in any state or county medical society.

Adjournment.

SIDNEY J. SHIPMAN, M.D., *Chairman*  
L. HENRY GARLAND, M.D., *Secretary*

## In Memoriam

ALLEN, CARLTON STEWART. Died in Los Angeles, May 4, 1948, age 64, of a heart attack. Graduate of the University of Southern California School of Medicine, Los Angeles, 1909. Licensed in California in 1909. Doctor Allen was a retired member of the Los Angeles County Medical Association and the California Medical Association.

KIRKPATRICK, JOSEPH HUNTER. Died in Los Angeles, March, 1948, age 77. Graduate of the Chicago Homeopathic Medical College, Illinois, 1897. Licensed in California in 1897. Doctor Kirkpatrick was a retired member of the Los Angeles County Medical Association and the California Medical Association.

LINDSAY, WILLIAM KINKADE. Died in Sacramento, May 5, 1948, age 71. Graduate of the University of California Medical School, Berkeley-San Francisco, 1901. Licensed in California in 1901. Doctor Lindsay was a retired member of the Sacramento Society for Medical Improvement and the California Medical Association.

MACK, CLIFFORD WILMOT. Died in Livermore, March 31, 1948, age 64. Graduate of the University of Michigan Medical School, Ann Arbor, 1908. Licensed in California in 1908. Doctor Mack was a member of the Alameda County Medical Association, the California Medical Association, and an Affiliate Fellow of the American Medical Association.

PHILIP, WILLIAM STEWART. Died in Pasadena, November 29, 1947, age 82. Graduate of McGill University Faculty of Medicine, Montreal, 1889. Licensed in California in 1896. Doctor Philip was a member of the Los Angeles County Medical Association, the California Medical Association, and a Fellow of the American Medical Association.

ROGERS, FRANCIS LLEWELLYN. Died in San Pedro, April 30, 1948, age 83, following an extended illness. Graduate of the State University of Iowa College of Medicine, Iowa City, 1891. Licensed in California in 1906. Doctor Rogers was a retired member of the Los Angeles County Medical Association and the California Medical Association.

SLEMONS, JOSIAH MORRIS. Died in Los Angeles, April 30, 1948, age 72. Graduate of Johns Hopkins University School of Medicine, Baltimore, Maryland, 1901. Licensed in California in 1913. Doctor Slemmons was a retired member of the Los Angeles County Medical Association and the California Medical Association.

SMILEY, HARRY WILBUR. Died in La Jolla, April, 1948, age 62. Graduate of the University of Arkansas School of Medicine, Little Rock, 1918. Licensed in California in 1920. Doctor Smiley was a retired member of the Riverside County Medical Society and the California Medical Association.

WOODS, RALPH A. Died in Mexico City, May 5, 1948, age 56, of a heart attack. Graduate of the University of Illinois College of Medicine, Chicago, Illinois, 1920. Licensed in California in 1920. Dr. Woods was a retired member of the Los Angeles County Medical Association and the California Medical Association.

# NEWS and NOTES

NATIONAL • STATE • COUNTY

## LOS ANGELES

Dr. Charles M. Carpenter, professor of infectious diseases in the School of Medicine on the Los Angeles campus of the University of California, has been elected chairman of the Medical Research Society of Southern California. The organization was recently formed to further high standards of medical research and education and to foster the public's interest in the present-day need of research. The group corresponds to a similar organization in Northern California.

Advisory council members are, Dr. Walter Macpherson, College of Medical Evangelists; Dr. B. O. Raulston, University of Southern California; Dr. Stafford L. Warren, University of California at Los Angeles, and Dr. Lewis T. Bullock.

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Dr. Ralph Schroeder has been elected president of the newly formed San Gabriel Valley branch of the Los Angeles County Medical Association. The new group is reported seeking county medical society sanction of its formation and of a proposal to take into membership doctors who are now members of the Pasadena-Alhambra and the East Los Angeles branches of the county organization. Dr. Samuel N. Smith is vice-president of the San Gabriel Valley group, and Dr. E. E. Wadsworth is secretary.

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Creation of the departments of Biophysics, Infectious Diseases, and Physical Chemistry in the new University of California at Los Angeles Medical School, and the appointments of 16 physicians to the faculty have been approved by the University of California Board of Regents. The appointees are Dr. Ernest H. J. Bors, Dr. Francis X. Byron, Dr. Roger O. Egeberg, Dr. Kathryn F. Fink, Dr. Robert M. Fink, Dr. Leo Kaplan, Dr. Wright H. Langham, Dr. William H. Leake, Dr. George M. Leiby, Dr. Charles W. McClanahan, Dr. Thomas H. Sternberg, Dr. George A. Stevens, Dr. George V. Taplin, Dr. Joseph A. Weinberg, Dr. Samuel J. Weinberg and Dr. Franklin B. Wilkins. Fifteen of the 16 physicians are associates with the Sawtelle and Birmingham Veterans Administration hospitals, whose teaching and research programs are to be coordinated with similar work at the new UCLA Medical School. Dr. Langham, a member of the staff of Los Alamos Scientific Laboratories, will integrate work on atomic medicine with the medical school's program.

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At the annual meeting of the Board of Trustees of the College of Medical Evangelists held May 17, 1948, Dr. George Tryon Harding, clinical professor of psychiatry at the Ohio State University College of Medicine, and Medical Director of the Harding Sanitarium in Columbus, Ohio, was elected president of the College of Medical Evangelists. Dr. Harding will take office September 1, 1948.

The Board of Trustees' report also announced that Dr. Walter E. Macpherson, for six years president of the College of Medical Evangelists and formerly its dean, will become vice-president of the College and chairman of the section on medicine.

Dr. Harding was born in Columbus, Ohio, in 1904, and graduated from the College of Medical Evangelists in 1928. At present he is a consultant in neuropsychiatry at the Children's Hospital, Grant Hospital, and University Hospital in



DR. GEORGE T. HARDING

Columbus, Ohio. He is a member of the board of trustees of the Franklin County Tuberculosis Hospital in Columbus, a past president of the Columbus Academy of Medicine, and former councilor of the Ohio State Medical Association.

He was certified by the American Board of Psychiatry in 1941, and is now an examiner on that Board. Dr. Harding is affiliated with the following medical organizations: a Fellow of the American Medical Association, the American Psychiatric Association, and the American College of Physicians; a member of the Association for Research in Nervous and Mental Disease, and of Central Neuropsychiatric Association; chairman of the Mental Hygiene Committee of the Ohio State Medical Association; past president of the Columbus Academy of Medicine; and special lecturer in psychiatry in the Graduate School of Medicine of the College of Medical Evangelists.

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The 34th Clinical Congress of the American College of Surgeons will be held in Los Angeles, with headquarters at the Biltmore Hotel, from October 18 to 22, 1948. The program of scientific sessions on subjects in the fields of general surgery; eye, ear, nose, and throat surgery; gynecology and obstetrics; urology; and orthopedic, thoracic, plastic, and neurological surgery, will be supplemented by operative

clinics in hospitals in Los Angeles and vicinity by showings of operations by television and motion pictures, and by a four-day hospital standardization conference for hospital personnel. Dr. Donald G. Tollefson of Los Angeles is chairman of the committee on arrangements.

#### SANTA CLARA

A venereal disease demonstration project, sponsored by the Palo Alto City, Santa Clara County, and San Jose City Health Departments; the County Medical Society; the State Department of Public Health; and the U. S. Public Health Service, is under way in Santa Clara County, the State Department of Public Health reports.

The purpose of the study is two-fold:

1. To demonstrate that strengthening of the private physician and health department relationship, as an essential of a sound venereal disease control program and upon a continuing basis, will result in increasing the number of patients under the care of private physicians.

2. To demonstrate that a public information program, integrated with the general health education program and upon a continuing basis, will result in accelerated case finding both for private physician and the health departments.

An executive committee is directing the project. Members of the committee are health officers Louis Olsen, Palo Alto; Dwight M. Bissell, M.D., San Jose; W. Elwyn Turner, M.D., Santa Clara County; and Joseph Donovan, Executive Secretary, Santa Clara County Medical Society. Dr. Turner is chairman of the committee.

#### CONTRA COSTA

Plans for formation of a countywide hospital district, which would spend \$4,500,000 for acquisition, construction and improvement of facilities throughout the county, recently received the endorsement of the Contra Costa Medical Society. The endorsement was contained in a letter to the county board of supervisors. The proposed program, which would carry out recommendations made by J. E. Hamilton and Associates, hired last year to make a survey of the county's needs, includes construction of a new 150-bed general hospital in Richmond at a cost of \$2,500,000 and a new 50-bed facility in the Walnut Creek-Lafayette area at a cost of \$875,000, purchase of the Pittsburg Community Hospital for about \$200,000 and purchase of the Martinez Community Hospital for around \$450,000. All facilities included in the plan would be administered by a non-profit organization and all county residents would have access to hospitalization at cost.

#### SISKIYOU

Bubonic plague has been demonstrated in fleas from squirrels collected by State Department of Public Health rodent survey crews in Siskiyou County. The squirrels were collected in April.

#### TULARE

A petition asking that the proposed Tulare District Hospital be made available to all licensed physicians and surgeons when it is ready for use was presented to the board of directors of the hospital district last month by Harry Bussard, D.O. He said that the petition had been signed by residents of the district "who feel that since the hospital is tax supported by them they should be privileged to have osteopathic physicians and surgeons available, as well as medical physicians and surgeons."

#### GENERAL

The California State Personnel Board announces examinations will be held August 3 for applicants for the positions of physicians and surgeon and senior physician and surgeon. Salary range for physician and surgeon is \$415 to \$505 a month, and for the senior position is \$530 to \$644 a month. Details of the requirements and description of the positions may be had from State Personnel Board, 1015 L Street, Sacramento.

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An appeal for doctors to fill vacancies anticipated in the medical branch of the Veterans Administration was made recently by H. H. Darling, M.D., acting Medical Director for the Branch 12 area, in a letter to the California Medical Association. Pointing out that the doctors who were assigned to the Veterans Administration from the Army and Navy at the end of the war soon will complete their obligated tour of military duty, Dr. Darling said that it will require a major effort to replace them. In Branch 12, he said, which encompasses California, Nevada, Arizona and Hawaii, "there is a critical need for anesthesiologists and men who are interested in tuberculosis."

Stressing the opportunities for young physicians, Dr. Darling called attention to a recent statement by Dr. Paul Magnuson, Chief Medical Director, in which he said: "I know of no place in the country, other than the Veterans Administration hospitals, where a man can practice 80 per cent of the time in a specialty after finishing a three-year residency." In relation to Dr. Magnuson's statement, Dr. Darling said that "in general, the specialty boards require that at least 80 per cent of a candidate's practice be devoted to a specialty for at least two years after completion of formal residency training."

"The compensation of doctors in the Veterans Administration is based directly on qualification," Dr. Darling said in his letter. "Original appointment is in the grade commensurate with the applicant's training and experience. There is no rigid organizational pyramid. Initial basic salaries range from a minimum of \$4,149.60 per annum for men who have had less than three years' experience, including internship and civil and military practice, to a maximum of \$9,975.00 per annum. There are statutory provisions for periodic increases in salary up to \$11,000.00 per annum for Diplomates of the American Specialty Boards, and \$10,000.00 for others. Board men, whatever their grades, receive a 25 per cent addition to the base pay, up to the statutory maximum. Some of our hospitals have quarters available with exceptionally low rental. Leave and retirement privileges are most liberal."

Doctors interested in further information concerning available opportunities in hospitals or out-patient clinics, either in Branch 12 or elsewhere in the United States, may communicate with Branch Medical Director, Veterans Administration Branch Office 12, 180 New Montgomery Street, San Francisco 5, California.

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A number of changes in requirements of the American Board of Obstetrics and Gynecology, Inc., were made at the annual meeting of the organization last month, according to an announcement by the Board. Bulletins now available for distribution upon application give details of all new regulations. These relate both to candidates and to hospitals conducting residency services for training.

The next scheduled examination (Part I) written examination and review of case histories, for all candidates will be held in various cities of the United States and Canada on Friday, February 4, 1949. Application may be made until November 1, 1948.

## BOOK REVIEWS

**DISEASES OF THE SKIN.** By Oliver S. Ormsby, M.D., Rush Professor of Dermatology Emeritus, University of Illinois, and Hamilton Montgomery, M.D., M.S., Associate Professor of Dermatology and Syphilology, Mayo Foundation for Medical Education and Research, Graduate School, University of Minnesota, Rochester. Seventh Edition. Lea & Febiger. 1948.

Ormsby's textbook, always the old reliable in dermatology, has been brought right up to date in this 1948 seventh edition. The authors have done a most thorough job of incorporating in it the recent advances in dermatology; almost every page indicates a thorough study of the newer and correct literature.

The junior author, particularly well known for his work in histopathology, has rendered an invaluable service by thoroughly covering the field of laboratory diagnosis.

The bibliography, carried at the bottom of the pages, is quite voluminous and hence of value for careful study of a given subject.

Every physician or student who is interested in dermatology-syphilology should have this new edition in his library.

**PSYCHOBIOLOGY AND PSYCHIATRY—A Textbook of Normal and Abnormal Human Behavior.** By Wendell Muncie, M.D., Practicing Psychiatrist; Chairman, Medical Advisory Board, Seton Institute, Baltimore, Md. Second Edition with 70 illustrations. The C. V. Mosby Company. 1948.

By far the most striking change in this edition from the first is the color of the cover from blue to red. In addition, by employing thinner paper and eliminating the lengthy historical survey at the end, the bulk of the volume has been materially reduced. The convulsive disorders have graduated to the dignity of chapter treatment, and an additional short chapter treats of newer physical treatment methods, namely shock and leucotomy. In other respects there is little difference in the two editions.

One might have hoped that one so closely associated with Adolf Meyer would present a clear and understandable exposition of this school of Psychiatry. In this reviewer's opinion this has unfortunately not been accomplished. One finishes this book with the firm opinion, in spite of the author's protestations to the contrary, that the main virtue of Psychobiology is its eclecticism, its greatest vice the introduction of still another terminology to confuse the student.

The presentation of case material to illustrate the various reaction types is excellent, and the special terminology of the Psychobiologist is sufficiently explained and paralleled with more familiar terms to clarify the classification in this regard.

Those conditions which it is now fashionable to consider as "psychosomatic" are given adequate treatment. The author remains non-committal in failing to give a definite opinion regarding the primary importance of specific constitutional and environmental factors in the production of these entities, which at the present time seems the wise and conservative thing to do.

**THE TREATMENT OF RHEUMATISM IN GENERAL PRACTICE.** By W. S. C. Copeman, M.D. Fourth Edition. The Williams & Wilkins Co. 1946.

This is the fourth edition of a book first published in 1933, and, as the author writes in his preface, makes no pretense of being a textbook. Even so, a wide range of subjects is included, some of which, e.g., the chapter on endocrines, could be deleted. Part I is a discussion of rheumatic fever, which omits mention of the relationship of streptococcal infection to this disease. The chapter on rheumatoid arthritis, only 17 pages, contains a wealth of information.

There are contradictory passages in different sections on diet and many drugs recommended which are no longer used by well-informed physicians in the United States. The book has little to recommend it to the general practitioner; the specialist on rheumatic disease will find in it some interesting material.

**EPILEPSY, The Annual Symposium of the Association for Research in Nervous and Mental Disease.** Proceedings of the Association held jointly with the International League against Epilepsy, December 13 and 14, 1946, New York. Research Publications Association for Research in Nervous and Mental Disease. Volume XXVI. Editorial Board, William G. Lennox, M.D., H. Houston Merritt, M.D., and Thomas E. Bamford, M.D. With 167 illustrations and 56 Tables. The Williams & Wilkins Company. 1947.

This book of 650 odd pages, 167 illustrations and 56 tables presents the latest studies and opinions on Epilepsy by the outstanding authorities on this subject in this country and abroad. The volume consists of 45 papers dealing with almost every phase of convulsive disorders, including sections on the historical aspects of the subject, heredity and pathology, experimental studies, electroencephalography, treatment, special contributions from the experience of the recent war and, finally, the psychological and social aspects of Epilepsy. Especially valuable are the questions, answers, comments and discussions appended to a high percentage of the contributions. The quality of this forum of discussion can be appreciated from the fact that the names of such authorities as Lennox, Penfield, Merritt, Walker, Gibbs, Fulton, Cobb, McCulloch and Jasper appear again and again.

As the third symposium on Epilepsy in the 26 annual meetings of the Association for Research in Nervous and Mental Disease since 1920, the volume amply reflects the wide interest and rapid advances made in this subject since the previous symposiums of 1922 and 1929. Particularly noteworthy are the contributions in three aspects of the subject; the physiological and biochemical basis of convulsive disorders as determined by experimental methods (17 contributions), the advances in both experimental and clinical studies made possible by electroencephalography (24 contributions) and the great advances in anti-convulsive therapy, which have been achieved by neurophysiological and experimental pharmacological methods (7 contributions).

From the standpoint of fundamental pathogenesis, the electrolyte studies of Colfer, the biochemical studies of Gurdjian, Webster and Stone and the biochemical and enzymatic studies of Pope, Morris, Jasper, Elliott and Penfield were of special interest. In another paper Penfield and Jasper propose and adduce evidence to support the interesting theory that the diencephalon is "the highest level" of cerebral function to which the cerebral cortices serve a subservient role. They propose that as a central system, the diencephalon acts to unify and integrate the activity of the more specialized cortical areas in the two hemispheres.

Experimental reproduction of the electroencephalographic pattern typical of petit mal was achieved by Jasper and Droogleever-Fortuyn by stimulation of the massa intermedia and by Chenoweth and St. John following the intravenous administration of fluoroacetic acid. Additional papers of electroencephalographic importance were the frequency analyzer of Grey Walter and the increased incidence of seizure discharges and epileptic foci in epileptic patients when the electroencephalographic recording was obtained by Gibbs and Gibbs with the patient asleep. The papers on Mesantoin by Kozol and by Loscalzo and on the tridione by Davis and Lennox were of particular interest to the pharmacologist and the neurologist.



Because of its character this volume would be of but limited interest to the medical student who might better approach the subject of Epilepsy in a more orderly fashion as presented in any of the several excellent neurological textbooks now available, as for example in "Diseases of the Nervous System" by Russell Brain. For the more advanced student and the physician concerned with the convulsive reactivity of his patients, the volume should prove both stimulating and rewarding. For the neurophysiologist, electroencephalographer, neurologist and neurological surgeon, the book definitely is a "must."

**OFFICE IMMUNOLOGY, including Allergy.** A Guide for the Practitioner. Edited by Marion B. Sulzberger and Rudolf L. Baer. Authors: Marion B. Sulzberger, M.D., Professor of Clinical Dermatology and Director, New York Skin and Cancer Unit, New York Postgraduate Medical School and Hospital; W. C. Spain, M.D., Clinical Professor of Medicine, New York Postgraduate Medical School and Hospital; Rudolf L. Baer, M.D., Instructor in Dermatology and Syphilology, New York Skin and Cancer Unit, New York Postgraduate School and Hospital; Abram Kanof, M.D., Adjunct Pediatrician, Jewish Hospital, Brooklyn; Alfred J. Well, M.D., Lederle Laboratories Division, American Cyanamid Company; Naomi M. Kanof, M.D., Associate Attending in Dermatology, Garfield Memorial and Children's Hospitals, Washington, D. C. The Year Book Publishers, Inc., Chicago. 1947. Price, \$6.50.

Office Immunology is a clinical handbook containing the essential information regarding immunologic procedures indispensable in the diagnosis and treatment of allergic and infectious diseases. The authors, combining the experience of the dermatologist, allergist, pediatrician and immunologist have selected with careful discrimination the material which should be included under this title. Controversial ideas and methods have been excluded. The immunologic procedures described, include only those which can be performed on the patient by the practicing physician without complicated laboratory facilities. The technics of performing the tests and the criteria for evaluation of results are described in detail.

The range of subject matter is indicated by the chapter headings. The book begins with two chapters devoted to descriptions of the common technics of diagnosis, prophylaxis and therapy. Then follows chapters on the immunology of infections; the immunologic principle of transfusion reactions and the Rh factor; the respiratory allergies; dermatologic immunology; immunologic management of spider, insect and snake bites; and finally a chapter on miscellaneous allergies. The chapter on infectious diseases contains not only the important facts on the diseases described, but also, a useful compilation of detailed specifications of immunologic preparations, including the name of the supplying firm, complete information regarding packaging, dosage schedules, etc.

Study of this book re-emphasizes the numerous and indispensable uses of immunologic methods in the day by day practice of medicine. Office Immunology is unique in the wide range of useful information included in one volume. It should be a useful addition to the desk library of the general practitioner, internist, dermatologist, pediatrician and even the allergist.

**HEADACHE AND OTHER PAIN.** By Harold G. Wolff, M.D., Professor of Medicine (Neurology) and Associate Professor of Psychiatry, Cornell University Medical College. Oxford University Press. 1948. \$12.00.

Considering the relative frequency of headache as a presenting symptom, the practitioner of medicine should be delighted by the advent of a treatise of over 600 pages devoted solely to this subject. Most of us are familiar with one or another aspect of the researches of the author and his coworkers on the general subject of pain. They have accomplished much in controlling experimental procedures in a

phenomenon which must, by definition, remain in the last analysis subjective.

The first part of the book deals with the mechanism of pain in general. Following this is an exhaustive treatment, from the experimental aspect, of pain-sensitive structures in the head, based on careful observations made during neurosurgical procedures. The remainder deals in detail with the type and mechanism of head pain in those conditions, varying from cerebral neoplasm to dental caries, in which headache is a striking symptom.

Migraine receives extensive treatment, both from the standpoint of the physiological mechanism of the production of its symptomatology and the personality structure in which it is prone to develop. For the consideration of this syndrome alone the book is well worth reading.

The author's approach to the subject is far from being confined to the theoretical; treatment of the patient is given adequate consideration. In all, the book can be highly recommended to the profession at large. For the neurologist and psychiatrist it is extremely valuable.

**HISTORY OF THE MEDICAL SOCIETY OF THE COUNTY OF WESTCHESTER, 1797-1947.** Published by the Medical Society of the County of Westchester, 1947. Cloth bound, 193 pages.

The history of this county medical society of over 1,000 members was published in honor of its one hundred and fiftieth anniversary, dedicated to its two past historians, and compiled by its present historian, Dr. Lawrence D. Redway.

The first county medical society in the state of New York began: "at a respectable Meeting of Physicians of the County of Westchester on the 8th day of May, 1797—at the House of William Barker in the White Plains—Present—" The names of the eight founding fathers followed.

The book is divided into two parts. Part I consists of an interesting historical sketch of the period prior to the society's inception and through it until 1922. Part II, the larger portion of the book, is devoted to a year-by-year factual report of the society's activities from 1922 to 1947, and includes the records of the articles of incorporation of the society and the reason therefor, at the surprisingly late date of 1935. Since the minutes of the society from 1779 to 1831 were unaccountably "lost," the records of its medical men and events for that period were gleaned from the newspapers of the county and from other sources.

The book is well annotated and documented and will be of inestimable value for future historical reference.

**THE ACUTE BACTERIAL DISEASES—Their Diagnosis and Treatment.** By Harry F. Dowling, M.D., F. A. C. P., Clinical Professor of Medicine, George Washington University; with the collaboration of Lewis K. Sweet, M.D., Chief Medical Officer in Pediatrics and Infectious Disease, Gallinger Municipal Hospital. W. B. Saunders Company. 1948. \$6.50.

Descriptions of the important bacterial infections currently available in medical textbooks are confusing and incomplete. None has segregated these important disorders on the basis of the etiological agents. This new book by Dowling is a most important contribution. A preliminary section is devoted to the principles of diagnosis and treatment of the acute bacterial infections. This is followed by a detailed consideration of the diseases caused by the various infectious agents.

Only minor criticisms of any part of the work are indicated. The treatment of subacute bacterial endocarditis is not described in sufficient detail in the light of present information. The type of renal lesion associated with sulfonamide therapy which is not caused by precipitation of crystals in the renal tubules but by a diffuse process presumably the result of sensitization to the drug, is not mentioned. This is a serious oversight since this complication cannot be prevented by increasing the flow of urine or by the administra-

tion of alkali. Recent developments in the field of penicillin therapy involving less frequent administration of the ordinary soluble form of the drug were not available at the time the book went to press.

This book should be in the library of all physicians and medical students. It will be of particular value to the latter group and to their teachers, since the information presented has not been readily available elsewhere.

**BERGEY'S MANUAL OF DETERMINATIVE BACTERIOLOGY.** Board of Editor-Trustees Robert S. Breed, New York State Experiment Station (Cornell University), Geneva, New York; E. G. D. Murray, McGill University, Montreal, Province Quebec, Canada; and A. Parker Hitchens, University of Pennsylvania, Philadelphia, Pennsylvania. Sixth Edition. The Williams & Wilkins Company. \$15.00.

The sixth edition of Bergey's Manual brings this well known and valuable guide to the classification of the bacteria up to date. The book has been expanded to include additional species and new information. An index of "Sources and Habitats" will be of particular value in the identification of unknown organisms. Inspection of several sections reveals the considerable confusion that still exists in regard to the delineation of species among the bacteria and viruses.

This volume is an essential tool for general bacteriologists. It is much less valuable for the medical bacteriologist since better and more usable descriptions of the human pathogens are available.

**HANDBOOK OF TREATMENT AND MEDICAL FORMULARY.** By Charles M. Bruber, Ph.D., M.D., Professor of Pharmacology, Jefferson Medical College, Philadelphia. F. A. Davis Company, Publishers, Philadelphia. 1948. \$7.00.

This book is written as a reference work and a guide in drug prescription therapy. Its reasons for being in existence are the rapid advance in drug therapy and the need for ready and concise reference on the part of the medical practitioner. Its intent is to assist the practitioner to recognize anachronistic medicine and to employ modern methods.

The conditions discussed are arranged alphabetically. There is abundant cross reference. The drugs used in treatment are usually given in the form of prescriptions. The prescriptions are written out in both English and Latin. (The author rightly assumes that the full Latin rendition will be instructive to many.) Doses are given in both the metric and apothecary systems.

As a summary of modern drug therapy—up to 1945 (there are few references past that year)—one may praise this book, even if one does not agree with all of the selection of remedies. For example, why should pellet implantation be the only form of testosterone therapy used for eunuchoidism and testosterone in oil the only form used in cryptorchidism? On the other hand, it is refreshing to read all through the treatment of abrasions of the skin and subcutaneous abscesses and see no recommendation of the old type of skin disinfectant; instead one is advised to make the wound as clean as possible, to cover it and to use penicillin or sulfathiazol topically.

It is a handy book to have in one's office.

**THE 1947 YEAR BOOK OF OBSTETRICS AND GYNECOLOGY.** Edited by J. P. Greenhill, B.S., M.D., F.A.C.S., Professor of Gynecology, Cook County Graduate School of Medicine. The Year Book Publishers, Chicago. \$3.75.

Testing one's familiarity with the current literature, it is a great stimulus to read every summary and comment of *The 1947 Year Book of Obstetrics and Gynecology* so ably edited by Dr. J. P. Greenhill. From the first article "Fibrous Nature of Human Cervix and Its Relation to Isthmic Segment in Gravid and Nongravid Uteri" by Danforth (which, by the way, is a real contribution to the literature on this infrequently discussed subject) to the last division on "Endocrinology," one finds a crystal-clear, brief summation and

comment on the world literature. The conservative attitude concerning the value of the hormone test for pregnancy, the use of Vitamin E in sterility, abortions, premature labor, the limitations of the application of estrogen therapy and the comments on his own article, make one feel that the author is sound and honest in his opinions. Even an editorial prerogative, however, should not extend to such a selective interpretation of the use of spinal anesthesia in obstetrics. As enthusiastic as one may become about local anesthesia and as adept as one may be in its application, it has not been accepted as the anesthetic of choice in most clinics outside of those of the "Chicago group."

The outstanding articles in obstetrics reviewed in this book are Danforth's chapter on "Physiology," Hertig's and Sheldon's "Hydatidiform Mole," "Pregnancy in Patient with Hypertensive Disease" by Chesley and Annitto, and also Brown's and Mengert's "Recognition of Midpelvic Contraction." In Gynecology the chapter on "Infertility" has many helpful suggestions. In the section on Operative Technique, Shaw's article on the "Anatomy of the Vagina" is extremely valuable. Under Malignant Tumors, the work on vaginal smears is completely reviewed and emphasis is definitely placed on its limitations.

The articles by Norman F. Miller and Emil Novak on Carcinoma of the Corpus and Uterus are outstanding and the comments are most valuable.

The author and the publisher are to be complimented again for this excellent survey and the obstetrician and gynecologist who did not read the current literature as it was published, can relieve his professional conscience by reading *The 1947 Year Book of Obstetrics and Gynecology*.

**CLINICAL TOXICOLOGY.** By Clinton H. Thienes, M.D., Ph.D., Professor of Pharmacology and Head of the Department of Pharmacology and Toxicology, School of Medicine, University of Southern California, Los Angeles, Calif., and Thomas J. Haley, Ph.D., Fellow in the Department of Pharmacology and Toxicology, School of Medicine, University of Southern California, Los Angeles. Second Edition. Enlarged and thoroughly revised, illustrated. Lea and Febiger. 1948.

This book is 64 pages longer than the senior author's first edition. The increases have been made in descriptive material and in the number of tests for identifying the new drugs such as dihydromorphinone (dilaudid), ephedrine isomers, demerol, etc. New tests for several old poisons are included. The new antihistamines, benadryl and pyribenzamine, are recommended for use in histamine poisoning; BAL (2,3-dithiolpropanol) for metallic poisoning. The new insecticide, D.D.T., is also described and treatment indicated. There are two long lists of reactions of leading sulfonamides. Poisoning from vitamins is not overlooked, the two chief offenders being thiamine (B<sub>1</sub>) and vitamin D.

This is more than a handy reference book on all aspects of poisons. There is a synopsis of all essential information about each drug. This is repetitious of the discussions in textbooks on pharmacology. The grouping of poisons according to their major toxic action is preserved from the first edition. The authors state that for each poison at least one of the treatments suggested should be available to the physician in time of emergency, and this seems to be adhered to throughout. Highly commendable features are sections devoted to chemical diagnosis, the tests being described with adequate discussions and details of use of apparatus and reagents, with remarks as to the limitations of and errors in devices, instruments, etc. There is also an appendix which describes the preparation of special reagents—information not readily found elsewhere.

While this book will be of interest chiefly to professional toxicologists, medico-legal experts, and clinical pathologists, there is enough in it of value to physicians in practice to justify having it on the office shelf of handy books.